VIRAL SUBVERSION OF THE IMMUNE SYSTEM

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Abstract: The continuous interactions between host and viruses during their co-evolution have shaped not only the immune system but also the countermeasures used by viruses. Studies in the last decade have described the diverse arrays of pathways and molecular targets that are used by viruses to elude immune detection or destruction, or both. These include targeting of pathways for major histocompatibility complex class I and class II antigen presentation, natural killer cell recognition, apoptosis, cytokine signalling, and complement activation. This paper provides an overview of the viral immune-evasion mechanisms described to date. It highlights the contribution of this field to our understanding of the immune system, and the importance of understanding this aspect of the biology of viral infection to develop efficacious and safe vaccines.

1. INTRODUCTION

The continuous interactions between hosts and viruses during their co-evolution have shaped not only the immune system but also the counter-measures used by viruses. The evasion strategies that viruses have devised are highly diverse, ranging from the passive to the active. Passive evasion strategies comprise hiding inside the infected host cell in a dormant form or creating a broad antigenetic diversity among the progeny virions during each replication cycle (as exploited, for example, by retroviruses), thus evading or staying one step ahead of the immune response. Active mechanisms include interferences with pathways for major histocompatibility complex (MHC)

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class I and class II antigen presentation, natural killer (NK) cell recognition, cytokine signalling, apoptosis of infected cells, and complement activation. In this review, the authors provide an overview of the different active mechanisms that viruses use to evade host immune responses. Due to space constraints, those mechanisms will be presented concisely in pairs of associated figures and tables. The basic concepts of the components of the immune system targeted by the viruses are described in the figures, while viral strategies are listed in the corresponding tables. To save space, viruses are cited using the abbreviations of the International Committee for Taxonomy of Viruses.

2. VIRAL INTERFERENCE WITH MHC CLASS I PATHWAY

CD8-positive cells play an important role in immunity against viruses. Just how important these cells are is demonstrated by the evolution of viral strategies for blocking the genesis or the display of viral peptide-MHC class I complexes on the surface of viral infected cells. To enhance the understanding of this field, the manner in which viral proteins are processed for recognition by virus-specific CD8+ T cells is briefly described (Figure 1). In the infected cells, peptides are generated from by-products of proteasomal degradation. Most of the substrates consist of defective ribosomal products (DRiPs). Peptides are then transported into the endoplasmic reticulum (ER) by the TAP protein. Here, MHC class I molecules are folded through the actions of general purpose molecular chaperones working with a dedicated chaperone (Tapasin) that tethers MHC class 1 to TAP. After peptide binding, MHC class I molecules dissociate from TAP, leave the ER and migrate to the plasma membrane through the Golgi complex. As viral peptide-MHC class I complexes accumulate on the cell surface, they have a greater chance of triggering activation by CD8+ T cells with a cognate receptor. Viruses have been shown to interfere with virtually every step of T cell antigen processing and presentation (Figure 1 and Table 1). The viral proteins involved in such mechanisms have been called VIPRs (pronounced “viper”) for viral proteins interfering with antigen presentation. They are listed in Table 1 together with their mechanism of action. For an excellent review on this subject, see that of Yewdell and Hill (2002).

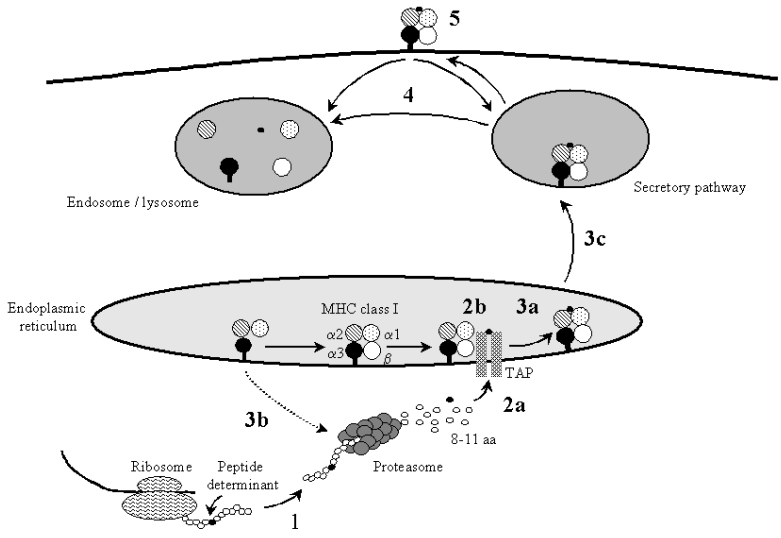

Figure 1. Viral interference with MHC class I pathway.

The classical MHC class I pathway is depicted with reference to viral interfering proteins listed in Table 1. Peptides are derived from DRiPs through the action of proteasomes and transported into the ER by the TAP protein. Nascent MHC class I molecules bind to TAP via tapasin. Binding of peptide to MHC class I molecules releases them from the ER. Peptide-MHC class I molecules then migrate to the cell surface. VIPRs have been shown to interfere with virtually every step of T cell antigen processing and presentation, namely (1) prevention of peptide degradation; (2) inhibition of peptide translocation in the ER, the inhibitory viral protein being either on the cytosolic side (2a) or in the lumen of the ER (2b); (3) retention of MHC class I molecules in the ER (3a) or in the transGolgi network (TGN) (3c), or by targeting of ER MHC class I molecules for degradation by the proteoasomes (3b); (4) reduction of peptide-MHC class I complexes exposed on the cell surface by inhibition of their migration to the cell surface, by increasing their endocytosis from the cell surface and by increasing their degradation into lysosomes; and (5) inhibition of T CD8+ cell recognition of cell surface peptide-MHC class I complexes. The VIPRs acting at those steps are listed in Table 1.

Table 1. Viral interference with the MHC class I pathway.

Site[(1)]	Virus[(2)]	Viral gene or protein	Mechanism of action	Source
1	HHV-4	EBNA-1	Contains a sequence that renders it resistant to proteasome degradation and self inhibition of synthesis	[1; 2]
1	HHV-5	UL83	Inhibits generation of antigenic peptides from a 72 kDa transcription factor by phosphorylation of the latter	[3]
2a	HHV-1 HHV-2	ICP47	Prevents peptide translocation by interacting with both TAP 1 and TAP 2 on the cytosolic side of the ER	[4; 5]
2a	BoHV-1	ICP47	Prevents peptide translocation by interacting with both TAP 1 and TAP 2 on the cytosolic side of the ER	[6]
2b	HHV-5	US6	Binds to TAP in the ER lumen and prevents peptide transport	[7; 8; 9]
3a	Adeno-virus	E19	Retains MHC-I in the ER by binding to the α1 and α2 regions (could also inhibit peptide loading of the MHC-I)	[10; 11; 12; 13]
3a	HHV-5	US3	Retains MHC-I in the ER	[14; 15]
3a	MuHV-1	m4	Forms extensive complexes with MHC-I in the ER	[16]
3b	HHV-5	US2, US3	Targets class 1 heavy chains for degradation by the proteasome	[17]
3b	MuHV-4	K3	Targets class 1 heavy chains for degradation by the proteasome and subverts TAP/Tapasin associated class I	[18; 19]
3b	HIV-1	Vpu	Destabilizes newly synthesized class 1 molecules and targets for degradation	[20]
3b	HTLV-1	p12(I)	Targets class 1 heavy chains for degradation by the proteasome	[21]
3c	MuHV-1	m152	Retains MHC-I within the ER-*trans*Golgi intermediate compartment	[22]
4	MuHV-1	m06	Prevents the MHC-I from reaching the cell surface	[23]
4	HIV, SIV	nef	Accelerates endocytosis of class 1 complexes (specific targeting of HLA A and B locus)	[24; 25]
4	EHV-1	?	Enhanced endocytosis of MHC-I from the surface	[26]
4	HHV-8	K3, K5	Targets the MHC-I to lysosomes	[27]
5	MuHV1	m4	Inhibits T CD8+ cell recognition	[28]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 1. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Levitskaya *et al*., 1995. [2] Yin, Maoury and Fahraeus, 2003. [3] Gilbert *et al*., 1993. [4] Galocha *et al.*, 1997. [5] Ahn *et al*., 1996. [6] Hinkley, Hill and Srikumaran, 1998. [7] Hengel *et al.,* 1996, 1997. [8] Ahn *et al*., 1997. [9] Lehner *et al*., 1997. [10] Cox, Bennink and Yewdell, 1991. [11] Burgert and Kvist, 1987. [12] Jefferies and Burgert, 1990. [13] Bennett *et al*., 1999. [14] Ahn *et al*., 1996. [15] Jones, *et al*., 1996. [16] Kavanagh, Koszinowski and Hill, 2001. [17] Wiertz *et al*., 1996. [18] Boname and Stevenson, 2001. [19] Lybarger *et al*., 2003. [20] Kerkau *et al*., 1997. [21] Johnson *et al*., 2001. [22] Ziegler *et al.,* 1997. [23] Reusch *et al*., 1999. [24] Le Gall *et al*., 1998. [25] Cohen *et al*., 1999. [26] Rappocciolo, Birch and Ellis, 2003. [27] Hewitt *et al*., 2002. [28] Kleijnen *et al*., 1997.

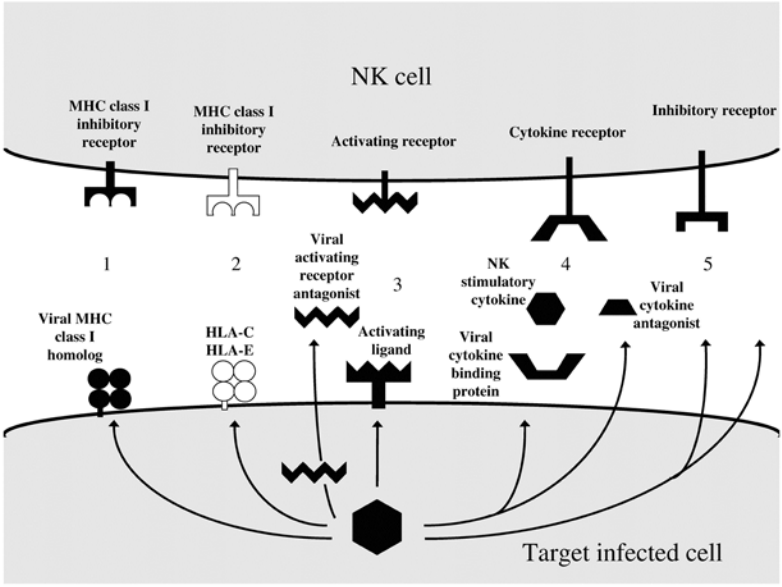

Figure 2. Viral evasion of NK cells.

Viral mechanisms interfering with NK cell functions fall into five categories, namely (1) expression of virally encoded MHC class I homologues that serve as NK cell decoys and ligate inhibitory receptors to block NK cytotoxicity; (2) selective modulation of MHC class I allele expression. Some viruses are able to down-regulate MHC class I molecules that are efficient for presentation of viral peptides to CD8+ cytotoxic T cells (such as HLA-A and HLA-B) without affecting or even increasing the expression of HLA-C and HLA-E, the dominant ligands for NK cell inhibitory receptors; (3) through the various mechanisms listed in Table 2, some viruses are capable of inhibiting the function of NK activatory receptor; (4) other viruses interfere with the cytokine pathways relevant to NK cell activation by producing virally encoded cytokine-binding proteins or cytokine antagonist; and (5) viruses can also directly inhibit NK cells by infecting them or by using viral envelope proteins to ligate NK cell inhibitory receptor.

3. VIRAL EVASION OF NATURAL KILLER CELLS

NK cells are lymphocytes that, in contrast to B and T cells, do not undergo genetic recombination events to increase their affinity for particular ligands, and are therefore considered as part of the innate immune system. They are capable of mediating cytotoxic activity and producing cytokines after ligation of a variety of germline-encoded receptors. Like CD8+ T cells, NK cells mediate direct lysis of target cells by releasing cytotoxic granules containing perforin and granzymes, or by binding to apoptosis-inducing receptors on the target cells. Several receptors that can activate NK cells have been identified, among which some recognize viral proteins (Orange *et al*., 2002). Due to the possible consequences of NK cell activation, normal host cells must inhibit NK activity. Various inhibitory receptors are consistently expressed by a subset of NK cells. These receptors bind to host MHC class I molecules and transmit inhibitory signals to the NK cells.

As noted above, many viruses have acquired effective means of avoiding T cell antigen presentation, thus avoiding T cell adaptive immune response. However, by eluding T cells, the viruses might have increased their susceptibility to NK cell-mediated defences. Consequently, in addition to the inhibition of T cell antigen presentation, some viruses have also acquired mechanisms to evade the action of NK cells. These mechanisms fall into five categories, presented in Figure 2; the viruses known to have acquired such mechanisms are listed Table 2. For an excellent review of the viral evasion of NK cells, see Orange *et al.* (2002).

Table 2. Viral evasion of natural killer cells.

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
1	HHV-5	UL18	Homologue of MHC class I, binds to ILT-2	[1; 2; 3; 4]
1	MuHV-1	m144	Homologue of MHC class I	[5; 6; 7]
1	MuHV-1	m157	Homologue of MHC class I, binds to Ly49-1	[8; 9; 10]
1	MuHV-2	r144	Homologue of MHC class I	[11]
1	MOCV	MC80R	Homologue of MHC class I	[12]
2	HHV-5	US2, US11	Cytosolic degradation of MHC class I, with exception of HLA-C and HLA-E	[13; 14; 15; 16]
2	HHV-5	US2, US3, US6, US11	Degradation or intracellular retention of MHC class I but not IL-18	[17]
2	HHV-5	UL40	Enhances surface expression of HLA-E	[18; 19; 20]
2	MuHV-1	m04	Forms complexes with MHC class I molecules intracellularly and on the cell surface	[21]
2	HIV	Nef	Induces the endocytosis of MHC class I with exception of HLA-C and HLA-E	[22; 23]

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
2	SIV	Nef	Induces the endocytosis of MHC class I with exception of HLA-C and/or HLA-E	[22; 24]
2	HHV-8	K5	Induces the endocytosis of HLA-A and HLA-B	[19; 25]
3	HHV-5	?	Decreases surface expression of the CD2 ligand LFA-3	[26]
3	HHV-5	UL16	Blocks the interaction of NKG2D-DAP10 and ULBP	[27; 28; 29]
3	MuHV-1	m152	Decreases surface expression of H60 (NKG2D ligand)	[30]
3	HHV-8	K5	Mediates ubiquitination and decreases surface expression of ICAM-1 and B7-2	[25; 31; 32]
3	HIV, HTLV	?	Mediates syalilation of cell surface receptors in infected cells	[33]
3	HIV	Tat	Inhibits LFA-1 mediated Ca^{2+} influx through binding of L-type Ca^{2+} channel	[34; 35]
4	MuHV-1	m131/129	Putative chemokine homologue	[36; 37]
4	HHV-8	vMIP-1, vMIP-2	Chemokine antagonists	[38; 39]
4	HHV-5	UL111a	Viral IL-10 homologue	[40]
4	HHV-4	BCRF1	Viral IL-10 homologue	[41]
4	ECTV	p13	IL-18 binding protein	[42]
4	MOCV	MC54L	IL-18 binding protein	[43]
4	HPV	E6, E7	IL-18 binding protein and antagonistic binding to IL-18 Rα	[44; 45]
4	MuHV-4	hvCKBP	Chemokine binding protein	[46]
4	VACV	vCKBP	Chemokine binding protein	[47]
5	HIV	/	Infects NK cells	[48]
5	HHV-1	/	Infects NK cells	[49]
5	HCV	E2	Binds to CD81	[50; 51]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 2. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Beck and Barrell, 1988. [2] Reyburn *et al*., 1997. [3] Leong *et al*., 1998. [4] Cosman *et al*., 1997. [5] Farrell *et al*., 1997. [6] Kubota *et al*., 1999. [7] Cretney *et al*., 1999. [8] Smith, Idris and Yokoyama, 2001. [9] Mandelboim *et al*., 2001. [10] Arase *et al*., 2002. [11] Kloover *et al*., 2002. [12] Senkevich and Moss, 1998. [13] Schust *et al*., 1998. [14] Gewurz *et al*., 2001. [15] Machold *et al*., 1997. [16] Lopez-Botet, Llano and Ortega, 2001. [17] Park *et al*., 2002. [18] Tomasec *et al*., 2000. [19] Ishido *et al*., 2000. [20] Wang *et al*., 2002. [21] Kavanagh *et al*., 2001. [22] Le Gall *et al*., 1998. [23] Cohen *et al*., 1999. [24] Swigut *et al*., 2000. [25] Coscoy, Sanchez and Ganem, 2001. [26] Fletcher, Prentice and Grundy, 1998. [27] Sutherland, Chalupny and Cosman, 2001. [28] Kubin *et al.,* 2001. [29] Cosman *et al.,* 2001. [30] Krmpotic *et al*., 2002. [31] Ishido *et al*., 2000. [32] Coscoy and Ganem, 2001. [33] Zheng and Zucker-Franklin, 1992. [34] Zocchi *et al*., 1998. [35] Poggi *et al*., 2002. [36] Fleming *et al*., 1999. [37] Saederup *et al*., 2001. [38] Kledal *et al*., 1997. [39] Inngjerdingen, Damaj and Maghazachi, 2001. [40] Kotenko *et al*., 2000. [41] Moore *et al*., 1990. [42] Born *et al*., 2000. [43] Xiang and Moss, 1999. [44] Lee *et al*., 2001. [45] Cho *et al*., 2001. [46] Parry *et al*., 2000. [47] Alcami *et al*., 1998. [48] Chehimi *et al.,* 1991. [49] York and Johnson, 1993. [50] Tseng and Klimpel, 2002. [51] Crotta *et al*., 2002.

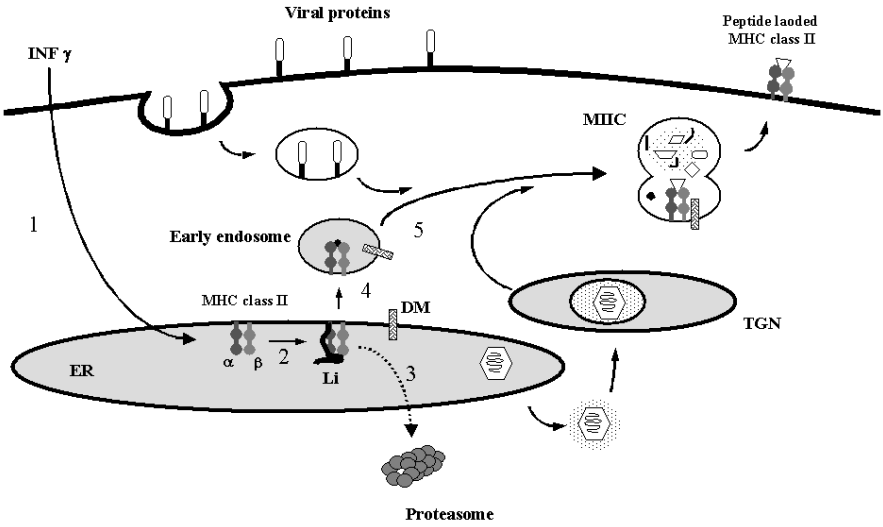

Figure 3. Viral inhibition of MHC class II antigen presentation.

MHC class II α and β chains and the invariant chain (Li) are expressed constitutively or in response to IFN-g stimulation. These molecules assemble in the ER to form the α-β-Li complexes that are then transported from the ER through the Golgi apparatus to the TGN, where the complexes are sorted to endosomes in response to signals present in the cytoplasmic tail of Li. In early endosomes, Li is progressively degraded by low-pH proteases so that fragments of it remain bound to the peptide-binding groove formed by the α-β chains. The MHC class II complexes then traffic into more acidic late endosomes and prelysosomal compartments known as MHC class II loading compartment (MIIC). Viral antigens can reach the endocytic pathway by phagocytosis, endocytosis or recycling of internal vesicules (site of virus assembly). Antigens delivered into the endocytic pathway are degraded by acid-dependent proteases to form peptides that are delivered to MIIC and loaded onto MHC class II α-β dimers. Exchange of peptide antigens for Li fragments occurs in collaboration with class II-like α-β dimers called DM. From the MIIC, peptide-loaded class II moves to the cell surface for presentation to CD4+ T cells. Viral mechanisms interfering with MHC class II antigen presentation fall into 5 categories: (1) inhibition of the IFN-γ transduction cascade leading to the expression of MHC class II; (2) Inhibition of the association of the α and β chains with the Li chains; (3) redirecting the α and b chains and DM for degradation by the proteasome; (4) preventing MHC class II from reaching the endocytic compartment; and (5) interfering with MHC class II processing and acidification of the endosome.

4. VIRAL INHIBITION OF MHC CLASS II ANTIGEN PRESENTATION

CD4-positive cells can recognize viral antigens expressed on virus-infected cells expressing MHC class II molecules to act cytolytically, to produce antiviral cytokines or to coordinate the antiviral immune response. MHC class II molecules are expressed constitutively by thymic epithelial cells, activated T cells and professional antigen-presenting cells, while in other cells, such as fibroblasts, keratinocytes, endothelial, epithelial and glial cells, their expression require IFN-γ stimulation. The latter induces the expression of MHC-II molecules through a complex cascade of factors (reviewed in Hegde, Chevalier and Johnson, 2003).

From the recent literature, it appears that viral inhibition of MHC class II antigen presentation is designed to prevent presentation of endogenous viral antigens in virus-infected cells rather than presentation of exogenous antigens in professional antigen-presenting cells.

Table 3. Viral inhibition of MHC class II antigen presentation.

Site (1)	Virus(2)	Viral gene	Mechanism of action	Source
1	Adeno-virus	E1A	Interferes with MHC class II upregulation (INF γ signal transduction cascade)	[1]
1	HHV-5	?	Interferes with MHC class II upregulation (INF γ signal transduction cascade)	[2; 3]
2	HHV-5	US3	Bounds to α/β subunits of MHC class II complexes in the ER reducing their association with Li	[4]
3	HHV-5	US2	Targets the MHC class II α and DM-α molecules for degradation by the proteasome	[5]
4	HHV-1	?	Redistributes MHC class II molecules away from the endocytic pathway	[6]
4	HIV	Env	Redistributes MHC class II molecules away from the endocytic pathway	[7]
5	HIV	Nef	Interference with MHC class II processing	[8]
5	SIV	Nef	Interference with MHC class II processing	[9]
5	HHV-1	gB	Interference with molecular co-players of MHC class II (DR and DM) processing	[10]
5	HPV/BPV	E5	Interference with MHC class II processing, and acidification of the endosomes	[11; 12]
5	BPV	E6	Interacts with AP-1, the TGN-specific clathrin adaptator complex	[11; 13]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 3. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Leonard and Sen, 1996. [2] Miller *et al*., 1999. [3] Miller *et al*., 1998. [4] Hegde *et al*., 2002. [5] Tomazin *et al*., 1999. [6] Lewandowski, Lo and Bloom, 1993. [7] Rakoff-Nahoum *et al*., 2001. [8] Stumptner-Cuvelette *et al.*, 2001. [9] Schindler *et al*., 2003. [10] Neumann, Eis-Hubinger and Koch, 2003. [11] Tortorella *et al*., 2000. [12] Andresson *et al*., 1995. [13] Tong *et al*., 1998.

To enhance the understanding of this field, Figure 3 illustrates how viral peptides are processed for presentation in association with MHC class II molecules on the surface of an infected host cell. Some of the viral mechanisms acquired by viruses to interfere with this process are listed in Table 3. For an excellent review of this topic, see Hegde, Chevalier and Johnson (2003).

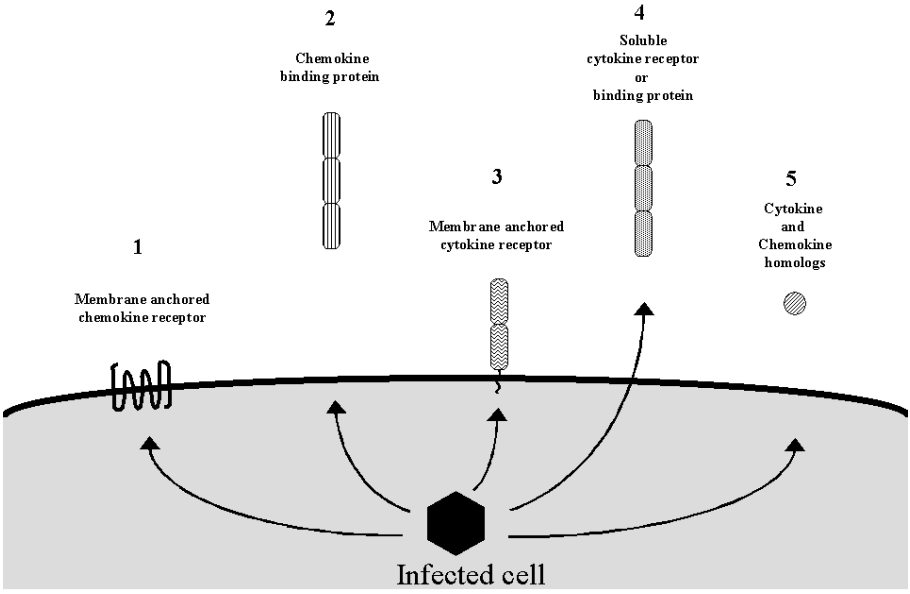

Figure 4. Viral interference with cytokines, chemokines and their receptors.

The strategies acquired by viruses to interfere with or to exploit host cytokines, chemokines and their receptors can be classified into 5 categories: (1) some viruses encode membrane anchored molecules able to bind host chemokine and eventually transduce a signal. Because these viral molecules have sequence similarity with host cellular receptors, they have been called chemokine receptors; (2) other viruses encode soluble proteins capable of binding to chemokines and preventing their action on target cells. Because these viral proteins are not homologues of host cellular proteins, they have been called chemokine binding protein rather than chemokine receptor; similarly, (3) viral encoded membrane anchored cytokine receptors; and (4) soluble cytokine receptors or soluble cytokine binding proteins have been described; (5) viruses are known to encode homologues of cytokines or chemokines.

5. VIRAL INTERFERENCE WITH CYTOKINES, CHEMOKINES AND THEIR RECEPTORS

Viral infection induces the production of cytokines and chemokines playing crucial roles in inducing the migration and activation of immune cells to areas of infection; in immune regulation; in anti-viral defence; as well as in the capacity of target cells to support virus replication. For example, cytokines such as interferons (IFN) and tumour necrosis factor (TNF) induce intracellular pathways that activate an anti-viral state or apoptosis, and thereby contribute to limit viral replication. A very large number of cytokines induce mechanisms that enhance immune recognition, or immune responses that protect against viral infection. Finally, some anti-viral cytokines mediate killing of infected cells by NK cells or cytotoxic T lymphocytes. Therefore, it is not surprising to find that cytokines, chemokines and their receptors are targets of viral immune-evasion strategies. The different strategies developed by viruses to interfere with or to exploit host cytokines, chemokines or their receptors are illustrated in Figure 4. Example of viruses known to have acquired such strategies are listed in the accompanying Table 4. For an excellent review of this topic, see the recent review by Alcami (2003).

Table 4. Viral interference with cytokines, chemokines and their receptors.

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
1	HHV-8	ORF74	Viral chemokine receptor, induces cell proliferation *in vitro* and tumours in transgenic mice	[1]
1	HHV-5	US28	Viral chemokine receptor	[2]
1	HHV-5	US27	Viral chemokine receptor	[3]
1	SCMV	E3-7	Cluster of five HCMV US28 homologues	[4]
1	MuHV-1	m33	Viral chemokine receptor	[5]
1	HHV-6	U51	Viral chemokine receptor	[6]
1	FWPV	FPV 021, 027, 206	Viral chemokine receptor	[7]
1	SWPV	SPV146	CXCR1 homologue	[3]
1	SPPV	Q2/3L	CC-chemokine receptor	[3]
1	YLDV	7L, 145R	CCR8 homologues	[8]
1	LSDV	LSDV011	CC-chemokine receptor homologue	[9]
2	EHV-1	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein	[10]
2	EHV-3	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein	[10]
2	BoHV-1	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein	[10]
2	BoHV-5	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC-chemokine binding protein	[10]

Site [1]	Virus[2]	Viral gene	Mechanism of action	Source
2	RanHV-1	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC- chemokine binding protein	[10]
2	CapHV-1	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC- chemokine binding protein	[10]
2	CerHV-1	gG (vCKBP4)	Secreted or membrane anchored C-, CC-, CXC- chemokine binding protein	[10]
3	MYXV	vCKBP1	Secreted C-, CC-, CXC- chemokine binding protein	[11]
3	VACV	vCKBP2	Secreted C-chemokine binding protein	[12; 13]
3	CPXV	H5R	Secreted C-chemokine binding protein	[12; 13]
3	MYXV	M-T1	Secreted C-chemokine binding protein	[12; 13]
3	MuHV-4	vCKBP3	Secreted C-, CC-, CXC-, CX_3C- chemokine binding protein	[14]
3	VACV	A41L	vCKBP2 homologue	[15]
4	HHV-5	UL144	Membrane TNFR homologue	[16]
5	CPXV	CrmB	Secreted TNF inhibitor	[17]
5	MYXV	MT-2	Secreted TNF inhibitor	[18]
5	CPXV	CrmC	Secreted TNF inhibitor	[19]
5	CPXV	CrmD	Secreted TNF inhibitor	[20]
5	CPXV	CrmE	Secreted TNF inhibitor, also expressed at the cell	[21]
5	VACV	CrmE	surface	[22]
5	LCDV1	ORF167L	Homology to domain of TNFR	[23]
5	SFV	T2	TNF-R homologue	[24; 25]
5	ECTV	E13	Secreted; blocks binding of CD30 to CD30L and induces reverse signalling in cells expressing CD30L	[26]
5	VACV	vCD30	Secreted; blocks binding of CD30 to CD30L and induces reverse signalling in cells expressing CD30L	[27]
5	VACV	B16R	Secreted receptor for interleukin-1 β	[28]
5	MYXV	MT-7	Secreted receptor for IFN-γ	[29]
5	VACV	B8R	Secreted receptor for IFN-γ	[30]
5	VACV	B19R	Secreted and cell surface binding protein for IFN-α/β	[31]
5	HHV-4	BARF1	Secreted binding protein for CSF1	[32]
5	ORFV	GIF	Secreted binding protein for GM-CSF/IL2	[33]
5	MOCV	MC54	Secreted binding protein for IL18	[34]
5	ECTV	E19	Secreted binding protein for IL18	[35]
5	MOCV	MC51, MC53	Secreted binding proteins for IL18	[36]
6	VACV	C11R	Viral epidermal growth factor homologue	[37]
6	ORFV	A2R	Viral vascular endothelial growth	[38]
6	HHV-4	BCRF1	Viral IL-10 homologue	[39]
6	HHV-5	UL111a	Viral IL-10 homologue	[40]
6	ORFV	vIL-10	Viral IL-10 homologue	[41]
6	EHV-2	E7	Viral IL-10 homologue	[42]
6	SaHV-2	ORF13	Viral IL-17 homologue	[43]
6	HHV-8	K2	Viral IL-6 homologue	[44]
6	VACV	A39R	Viral semaphorin, binds semaphorin receptor VESPR	[45]

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
6	FWPV	FPV080	Viral TGF-β homologue	[7]
6	FWPV	FPV072, FPV076	Viral β-NGF homologue	[7]
6	HHV-8	K6	Viral CR8 agonist	[46]
6	HHV-8	K4	C-, CC-, CXC-, CX3C-chemokine antagonist	[47]
6	HHV-8	K4.1	CCR4 agonist	[48]
6	HHV-6	U83	CC-chemokine agonist	[49]
6	MOCV	MC148	CC-, CXC-chemokine antagonist, CCR8 specific antagonist	[50; 51]
6	MuHV-1	m131/129	CC-chemokine agonist	[52 – 54]
6	HHV-5	UL146	CXCR2 agonist	[55]
6	GaHV-2	MDV003	CXC chemokine	[56]
6	HIV	tat	Partial chemokine similarity	[57]
6	HRSV	gG	Partial chemokine similarity, CX_3CL1 activity	[58]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 4. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Arvanitakis *et al*., 1997. [2] Bodaghi *et al*., 1998. [3] Murphy, 2001. [4] Alcami, 2003. [5] Davis-Poynter *et al*., 1997. [6] Milne *et al*., 2000. [7] Alfonso *et al.,* 1996. [8] Lee, Essani and Smith, 2001. [9] Tulman *et al*., 2001. [10] Bryant *et al*., 2003. [11] Mossman *et al.,* 1996. [12] Smith *et al*., 1997. [13] Graham *et al*., 1997. [14] Parry *et al*., 2000. [15] Ng *et al*., 2001. [16] Benedict *et al*., 1999. [17] Hu, Smith and Pickup, 1994. [18] Macen *et al.,* 1996. [19] Smith *et al.,* 1996. [20] Loparev *et al*., 1998. [21] Saraiva and Alcami, 2001. [22] Reading, Khanna and Smith, 2002. [23] Tidona and Darai, 1997. [24] Smith *et al*., 1990. [25] Smith *et al*., 1991. [26] Saraiva *et al*., 2002. [27] Panus *et al*., 2002. [28] Alcami and Smith, 1992. [29] Upton, Mossman and McFadden, 1992. [30] Alcami and Smith, 1995. [31] Colamonici *et al*., 1995. [32] Strockbine *et al.,* 1998. [33] Deane *et al*., 2000. [34] Xiang and Moss, 1999a. [35] Smith, Bryant and Alcami, 2000. [36] Xiang and Moss, 1999b. [37] Twardzik *et al.,* 1985. [38] Meyer *et al*., 1999. [39] Hsu *et al*., 1990. [40] Kotenko *et al*., 2000. [41] Fleming *et al*., 1997. [42] Rode *et al*., 1993. [43] Yao *et al*., 1995. [44] Aoki *et al.,* 1999. [45] Gardner *et al*., 2001. [46] Boshoff *et al*., 1997. [47] Kledal *et al*., 1997. [48] Stine *et al*., 2000. [49] Zou *et al.,* 1999. [50] Krathwohl *et al*., 1997. [51] Luttichau *et al*., 2000. [52] Fleming *et al*., 1999. [53] Saederup *et al*., 2001. [54] Saederup *et al*., 1999. [55] Penfold *et al*., 1999. [56] Parcells *et al.,* 2001. [57] Albini *et al*., 1998. [58] Tripp *et al*., 2001.

6. VIRAL MANIPULATION OF THE CELL DEATH PROGRAMME

Replication of viruses may stimulate suicide of the host cell directly or via recognition by immune effector cells. These cells (cytolytic T cells and NK cells) induce cell death by secretion of cytotoxic cytokines such as TNFs and by processes requiring direct cell-cell contact, such as release of perforin and granzyme. This form of programmed cell death is called apoptosis. Apoptosis is an orchestrated biochemical process that leads ultimately to the demise of the cell, initiated by both internal sensors (intrinsic pathway,

mitochondria dependent) and external stimuli (extrinsic pathway, death receptor mediated).

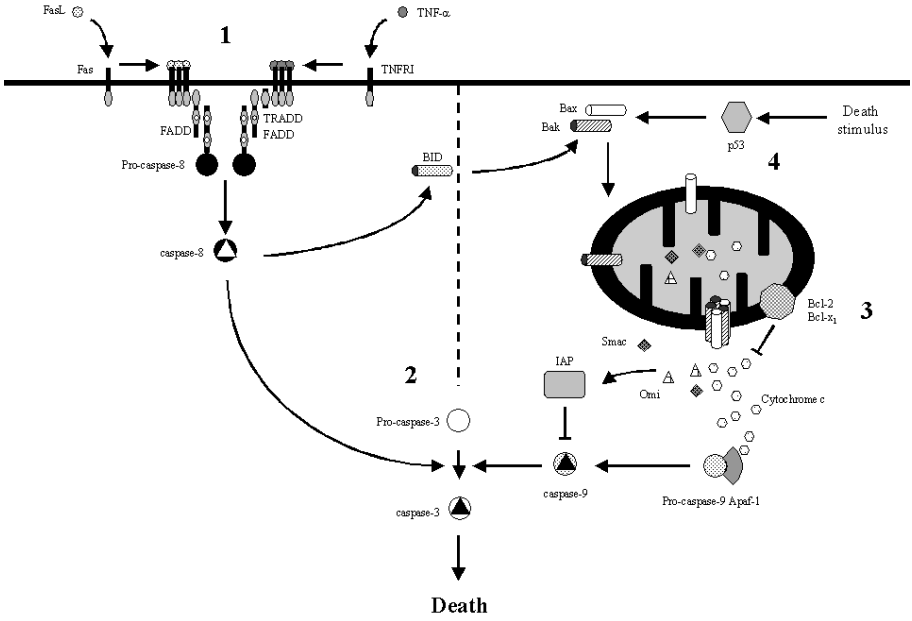

Figure 5. Viral inhibition of apoptosis.

Apoptosis can be initiated by two main pathways. The extrinsic pathway is triggered by death ligands binding to their cognate death receptors. These receptors then multimerize and their death domains (DDs) interact with the DDs of adaptator proteins that bind to pro-caspase 8 and/or pro-caspase 10 to form the DISC. This ends with pro-caspase cleavage in their active form. These caspases can then cleave Bid and activate the effector caspase cascade. On the other end, internal sensors initiate the intrinsic pathway via a process that results in hetero-oligomeric pores formation in the outer membrane of the mitochondria. Factors such as cytochrom c, Smac and Omi are then released in the cytoplasm where cytochrom c promotes formation of the apoptosome, resulting in autocatalytic activation of caspase 9, which initiates the effector caspase cascade. Caspases activation is negatively regulated by IAP, which are counter-balanced by proapoptotic Smac and Omi. Viral mechanisms of apoptosis inhibition fall into 4 main categories: (1) modulating of death receptors signalling; (2) regulation of caspase; (3) mimicking Bcl-2; and (4) blinding the internal sensors.

In the case of replicating viruses, apoptosis can be viewed as an altruistic defence mechanism by which the host infected cell commits suicide in order to prevent virus spread in the infected host. Indeed, premature cell death would enable viruses to maximally replicate or to establish latency. Apoptosis is a complex and highly regulated process. Many viruses have acquired mechanisms to inhibit this important biological process, by

targeting different steps. These mechanisms of viral inhibition of apoptosis can be classified into four main classes: modulation of death receptor signalling; caspase regulation; Bcl-2 mimicking; and internal sensors blinding. They are described in Figure 5. Viral proteins inhibiting apoptosis are listed in Table 5, together with their mechanism of action. For an excellent review of this subject, see Benedict, Norris and Ware (2002).

Table 5. Viral inhibition of apoptosis.

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
1	adeno-virus	E3-6.7	Complexes with 10.4 and 14.5 resulting in downmodulation of TRAIL receptor 1 and 2	[1]
1	adeno-virus	E3-10.4	Inhibits TNF and FasL induced apoptosis	[2; 3]
1	adeno-virus	E3-14.5	Inhibits TNF and FasL induced apoptosis	[2; 3]
1	adeno-virus	E3-14.7	Inhibits TNF induced apoptosis	[4; 5]
1	BoHV-4	ORF71	Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP)	[6]
1	EHV-2	E8	Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP)	[7]
1	SaHV-2	ORF71	Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP)	[8]
1	HHV-8	K13	Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP)	[9]
1	MOCV	MC159	Inhibits TNF and FasL induced apoptosis (viral homologue of cFLIP)	[7; 10]
1	HHV-5	UL36	Prevents caspase 8 activation	[11]
1	MYXV	MT-2	TNF-R homologue	[12; 13]
1	HHV-4	LMP1	Interacts with TRFAFs and TRADD	[14; 15]
1	SFV	T2	TNF-R homologue	[16; 17]
1	VACV	CrmE	TNF-receptor	[18]
1	CPXV	CrmB	TNF-receptor	[19]
1	CPXV	CrmC	TNF-receptor	[20]
1	CPXV	CrmD	TNF-receptor	[21]
1	CPXV	CrmE	Secreted TNF inhibitor, also expressed at the cell surface	[22]
1	LCDV1	ORF167L	Homology to domain of TNFR	[23]
1	HHV-5	UL144	Membrane TNFR homologue	[24]
2	ASFV	A224L	IAP-related protein	[25; 26]
2	Baculo-virus	P35	Inhibits caspase 1, 3, 6, 8 and 10	[27 – 29]
2	Baculo-virus	IAP	Inhibits caspase 3, 6 and 7	[27; 30]
2	CPXV	CrmA	Inhibits caspase 1, 4, 5 and 11	[31 – 33]
2	VACV	SPI-2	Inhibits caspase 1, 4, 5 and 11	[34]
2	ECTV	SPI-2	Inhibits caspase 1, 4, 5 and 11	[35]

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
3	Adeno-virus	E1B-19K	Bcl-2-related protein	[36; 37]
3	HHV-4	BHRF1	Bcl-2-related protein	[38; 39]
3	HHV-4	BALF1	Bcl-2-related protein	[40]
3	HHV-8	HHV-8 vBcl-2	Bcl-2-related protein	[41]
3	SaHV-2	ORF16	Bcl-2-related protein	[42; 43]
3	MuHV-4	m11	Bcl-2-related protein	[44]
3	ASFV	A179L	Bcl-2-related protein	[45]
3	HHV-1	US3	Prevents virus induced apoptosis via a post-translational modification of Bad	[46]
3	HHV-1	US5	Cooperates with US3	[46]
3	HHV-5	UL37	Appears to be functionally similar to Bcl-2	[47]
3	HHV-4	LMP1	Up-regulates Bcl-2 and other cell survival proteins	[14; 15]
3	HIV	Nef	Prevents apoptosis via phosphorylation of Bad	[48]
3	HTLV-1	Tax	Activates the Bcl-x_L promoter while repressing transcription of Bax	[49]
4	Adeno-virus	E1B-55K	Binds to p53 and functionally inactivates it	[50]
4	HPV	E6	Targets p53 for degradation	[51 – 53]
4	SV-40	Large T	Binds to p53 and inactivates it	[54; 55]
4	HBV	pX	Complexes p53 and inhibits p53-mediated transcriptional activation	[56]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 5. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Benedict *et al*., 2001. [2] Gooding *et al*., 1991. [3] Shisler *et al.,* 1997. [4] Gooding *et al*., 1988. [5] Li, Kang and Horowitz, 1998. [6] Wang *et al.,* 1997. [7] Bertin *et al.*, 1997. [8] Glykofrydes *et al*., 2000. [9] Sturzl *et al.,* 1999. [10] Shisler and Moss, 2001. [11] Skaletskaya *et al.,* 2001. [12] Macen *et al.,* 1996. [13] Xu, Nash and McFadden, 2000. [14] Kawanishi, 1997. [15] Henderson *et al.,* 1991. [16] Smith *et al*., 1990. [17] Smith *et al*., 1991. [18] Reading, Khanna and Smith, 2002. [19] Hu, Smith and Pickup, 1994. [20] Smith *et al.,* 1996. [21] Loparev *et al*., 1998. [22] Saraiva and Alcami, 2001. [23] Tidona and Darai, 1997. [24] Benedict *et al*., 1999. [25] Chacon *et al.*, 1995. [26] Nogal *et al.*, 2001. [27] Clem, 2001. [28] Clem, Fechheimer and Miller, 1991. [29] Bertin *et al.*, 1996. [30] Crook, Clem and Miller, 1993. [31] Dbaibo and Hannun, 1998. [32] Tewari and Dixit, 1995. [33] Zhou *et al.*, 1997. [34] Dobbelstein and Shenk, 1996. [35] Turner *et al.*, 2000. [36] Sundararajan and White, 2001. [37] Henry *et al.*, 2002. [38] Henderson *et al.*, 1993. [39] Kawanishi, 1997. [40] Marshall *et al.*, 1999. [41] Sarid *et al.*, 1997. [42] Nava *et al.*, 1997. [43] Derfuss *et al.*, 1998. [44] Wang, Garvey and Cohen, 1999. [45] Afonso *et al.,* 1996. [46] Jerome *et al.,* 1999. [47] Goldmacher *et al.*, 1999. [48] Wolf *et al.*, 2001. [49] Tsukahara *et al.*, 1999. [50] Teodoro and Branton, 1997. [51] Thomas and Banks, 1998. [52] Thomas and Banks, 1999. [53] Pan and Griep, 1995. [54] Lane and Crawford, 1979. [55] Linzer and Levine, 1979. [56] Wang *et al.*, 1995.

7. VIRUS COMPLEMENT-EVASION STRATEGIES

Complement is part of the innate immune system and is activated in a cascade manner through two main pathways, known as the classical and the alternative, and illustrated in Figure 6.

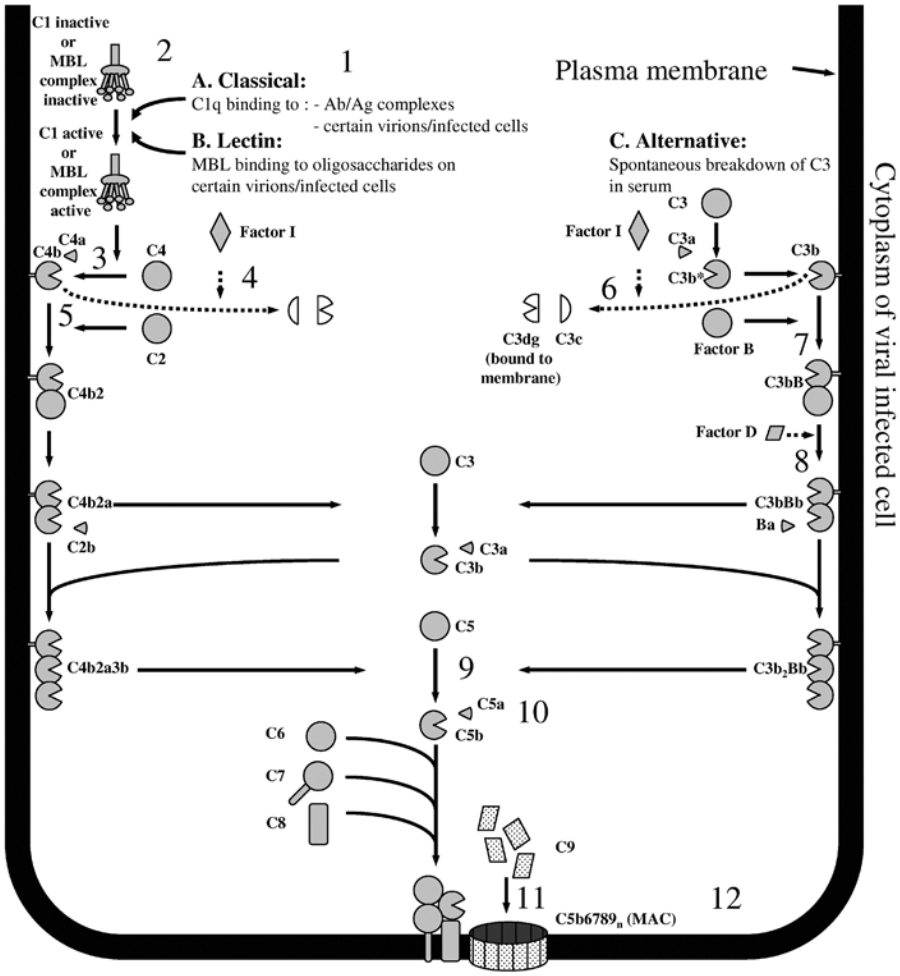

Figure 6. Virus complement evasion strategies.

Complement is part of the innate immune system and is activated in a cascade manner through two main pathways, known as the classical and the alternative pathways. The classical pathway is activated by the recognition proteins C1q or mannose-binding lectin, which bind respectively to charge clusters or neutral sugars on targets. In contrast, activation of the alternative pathway is a default process that proceeds unless down-regulated by specific mechanisms. Complement activation results in cleavage and activation of C3 and deposition

of opsonic C3 fragments on surfaces. Subsequent cleavage of C5 leads to assembly of the membrane attack complex (C5b,6,7,8,9), which disrupts lipid bilayers. Viruses have developed different strategies acting at different stages of the complement cascade in order to evade complement-mediated destruction. These are listed in Table 6, and are referred to in this figure. These strategies fall into three main categories: (1) some viruses interfere with the classical pathway by avoiding complement binding to antibody-antigen complexes, either by shedding or internalization of these complexes from the cell surface or by expressing virally-encoded Fc receptor on the cell surface; (2) other viruses encode and express functional homologue of cellular regulators of complement activation (RCA), protecting their lipid envelope and the membrane of the infected cell; and (3) some viruses can incorporate host complement RCA in their envelope and/or up-regulate expression of these proteins in infected cells.

Complement activation on host cells is prevented by several membrane regulators of complement activation (RCA), the activity of which is predominantly restricted to complement of the same species, a phenomenon called homologous restriction. These proteins down-regulate complement activity at two steps in the classical and the alternative pathways: complement receptor 1 (CD35) and decay-accelerating factor (CD55) inhibit the formation and accelerate the decay of the classical pathway and alternative pathway C3-activating enzymes (C3 convertases); complement receptor 1 and membrane cofactor protein (CD46) act as cofactors for Factor I (a serum protease), which catabolizes C4b and C3b, thereby inhibiting formation of the C3 convertases C4b2a and C3bBb; finally, at the end of the complement cascade, CD59 and possibly also homologous restriction factor (C8-binding protein) prevent the formation of the membrane attack complex.

In general, micro-organisms lack mammalian RCA and thus cannot restrict complement deposition and amplification on their surfaces. However, the toxicity of the complement system has selected viruses that have acquired countermeasures. The viral strategies to evade complement-mediated destruction are summarized in Table 6. For a recent review of this topic, see that of Favoreel *et al*. (2003).

Table 6. Virus complement-evasion strategies.

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
1	SuHV-1	gE-gI	Shedding of viral protein-antibody complexes	[1]
1	SuHV-1	gB-gD	Internalization of viral protein-antibody complexes	[2]
2	HHV-1	gE-gI	Fc receptor activity	[3]
2	HHV-3	gE-gI	Fc receptor activity	[4]
2	SuHV-1	gE-gI	Fc receptor activity	[1]
2	HHV-5	UL118-UL119	Fc receptor activity	[5]
2	HHV-5	TRL11/IRL11	Fc receptor activity	[6]
2	MuHV-1	Fcr1	Fc receptor activity	[7]

Site [(1)]	Virus[(2)]	Viral gene	Mechanism of action	Source
2	S	TGEV	Fc receptor activity	[8]
2	S	MHV	Fc receptor activity	[8]
2	S	BCoV	Fc receptor activity	[8]
3	CPXV	IMP	Downregulates chemotactic proteins C3a, C4a, C5a	[9]
4	VACV	VCP	Cofactor for factor I	[10]
4	VARV	SPICE	Cofactor for factor I	[11]
5	VACV	VCP	Binds to C4b	[10]
5	VARV	SPICE	Binds to C4b	[11]
5	SaHV-2	ORF4	Inhibits formation and accelerates decay of classical and alternative C3 convertases	[12]
6	VACV	VCP	Cofactor for factor I	[10]
6	VARV	SPICE	Cofactor for factor I	[11]
6	HHV-4	?	Cofactor for factor I?	[13]
7	HHV-1, HHV-2	gC1, gC2	Binds human C3b	[14]
7	VACV	VCP	Binds to C3b	[10]
7	VARV	SPICE	Binds to C3b	[11]
7	SaHV-2	ORF4	Inhibits formation and accelerates decay of classical and alternative C3 convertases	[12]
7	SuHV-1	gC	Binds species-specific C3b	[15]
7	BoHV-1	gC	Binds species-specific C3b	[15]
7	EHV-1	gC	Binds species-specific C3b	[15]
7	EHV-2	gC	Binds species-specific C3b	[15]
8	HHV-1	gC1	Inhibits Factor D binding	[16]
9	HHV-1	gC1	Inhibits C5 binding	[16]
10	CPXV	IMP	Downregulates chemotactic proteins C3a, C4a, C5a	[9]
11	SaHV-2	ORF15	Homologue of CD59	[17]
12	HHV-5	?	Upregulation of CD55 and CD46	[18]
12	SuHV-2	?	Incorporation of cellular complement regulators	[19]
12	VACV	?	Incorporation of cellular complement regulators	[20]
12	HIV	?	Incorporation of cellular complement regulators	[21]
12	HTLV	?	Incorporation of cellular complement regulators	[22]
12	SINV	?	Incorporation of sialic acids	[23]

NOTES: (1) Site of action. Numbers refer to paths identified in Figure 6. (2) International Committee for Taxonomy of Viruses (ICTV) abbreviations.

SOURCES: [1] Favoreel *et al.*, 1997. [2] Favoreel *et al.*, 1999. [3] Watkins, 1964. [4] Ogata and Shigeta, 1979. [5] Lilley, Ploegh and Tirabassi, 2001. [6] Atalay *et al.*, 2002. [7] Thale *et al.*, 1994. [8] Oleszak *et al.*, 1993. [9] Howard *et al.*, 1998. [10] Kotwal *et al.*, 1990. [11] Rosengard *et al.*, 2002. [12] Fodor *et al.*, 1995. [13] Mold *et al.*, 1988. [14] Friedman *et al.,* 1984. [15] Huemer *et al.*, 1993. [16] Kostavasili *et al.*, 1997. [17] Rother *et al.*, 1994. [18] Spiller *et al.*, 1996. [19] Maeda *et al.*, 2002. [20] Vanderplasschen *et al.,* 1998. [21] Saifuddin *et al.*, 1995. [22] Spear *et al.*, 1995. [23] Hirsch, Griffin and Winkelstein, 1981.

8. CONCLUSION

During the millions of years they have been co-evolving with their host, viruses have learned how to manipulate host immune control mechanisms. The review of the immune evasion strategies acquired by viruses revealed several fascinating aspects of this field. First, it is remarkable that individual virus families have targeted many common immunological principles. Second, the analysis of viral immunoregulatory proteins revealed that they belong to two classes: those encoded by genes with and those encoded by genes without sequence homology to cellular genes. While the former indicates that viruses have "stolen" genes from the host that were subsequently modified for the benefit of the virus, the latter suggests acquisitions through a mechanism of convergent evolution.

Viruses are obligate parasites that live "on the edge". On the one hand, they need to impair the immune response of their host to be able to replicate and to avoid eradication; but, on the other hand, they need to respect the host immune response in order to ensure their host's (and hence their own) survival. In other words, the perfect adaptation of a virus to its host would represent a virus able to complete its biological cycle without inducing clinical symptoms. Further studies are required to determine the roles of viral immune-evasion mechanisms in this delicate equilibrium. Indeed, most of the studies cited in this review have investigated the ability of viral genes to interfere with the host immune response *in vitro*. However, only *in vivo* experiments will be able to determine the real biological functions of these viral immune-evasion mechanisms. A beautiful example supporting this statement has been provided by the study of vaccinia virus IL-1β receptor. Indeed, while this viral product was thought to contribute to the pathogenicity of the virus, it is interesting to observe that deletion of the corresponding gene enhanced virus virulence and the onset of fever, suggesting that the purpose of a least some of the immune-evasion mechanisms is to reduce immunopathology caused by viral infection (Alcami and Smith, 1996).

In conclusion, this review highlights the complexity and the importance of viral immune-evasion strategies in the host-virus relationship.

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REFERENCES

Ahn, K., Gruhler, A., Galocha, B., Jones, T.R., Wiertz, E.J.H.J., Ploegh, H.L., Peterson, P.A., Yang, Y. & Fruh, K. 1997. The EER-luminal domain of the HCMV glycoprotein US6 inhibits peptide translocation by TAP. *Immunity,* **6:** 613–621.

Ahn, K., Meyer, T.H., Uebel, S., Sempe, P., Djaballah, H., Yang, Y., Peterson, P.A., Fruh, K. & Tampe, R. 1996. Molecular mechanism and species specificity of TAP inhibition by herpes simplex virus protein ICP47. *EMBO Journal,* **15:** 3247–3255.

Ahn, K.S., Agulo, A., Ghazal, P., Peterson, P.A., Yang, Y. & Fruh, K. 1996. Human cytomegalovirus inhibits antigen presentation by a sequential multistep process. *Proceedings of the National Academy of Sciences, USA,* **93:** 10990–10995.

Albini, A., Ferrini, S., Benelli, R., Sforzini, S., Giunciuglio, D., Aluigi, M.G., Proudfoot, A.E.I., Alouani, S., Wells, T.N.C., Mariani, G., Rabin, R.L., Farber, J.M. & Noonan, D.M. 1998. HIV-1 Tat protein mimicry of chemokines. *Proceedings of the National Academy of Sciences, USA,* **95:** 13153–13158.

Alcami, A. 2003. Viral mimicry of cytokines, chemokines and their receptors. *Nature Reviews Immunology,* **3:** 36–50.

Alcami, A. & Smith, G.L. 1992. A soluble receptor for interleukin-1-beta encoded by vaccinia virus – a novel mechanism of virus modulation of the host response to infection. *Cell,* **71:** 153–167.

Alcami, A. & Smith, G.L. 1995. Vaccinia, cowpox, and camelpox viruses encode soluble gamma-interferon receptors with novel broad species specificity. *Journal of Virology,* **69:** 4633–4639.

Alcami, A. & Smith, G.L. 1996. A mechanism for the inhibition of fever by a virus. *Proceedings of the National Academy of Sciences, USA,* **93:** 11029–11034.

Alcami, A., Symons, J.A., Collins, P.D., Williams, T.J. & Smith, G.L. 1998. Blockade of chemokine activity by a soluble chemokine binding protein from vaccinia virus. *Journal of Immunology,* **160:** 624–633.

Alfonso, C.L., Neilan, J.G., Kutish, G.H. & Rock, D.L. 1996. An African swine fever virus Bcl-2 homolog, 5-HL, suppresses apoptotic cell death. *Journal of Virology,* **70:** 4858–4863.

Andresson, T., Sparkowski, J., Goldstein, D.J., & Schlegel, R. 1995. Vacuolar H+ATPase mutants transform cells and define a binding site for the papillomavirus E5 on oncoprotein. *Journal of Biological Chemistry,* **270:** 6830–6837.

Aoki, Y., Jaffe, E.S., Chang, Y., Jones, K., Teruya-Feldstein, J., Moore, P.S. & Tosato, G. 1999. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. *Blood,* **83:** 4034–4043.

Arase, H., Mocarski, E.S., Campbell, A.E., Hill, A.B. & Lanier, L.L. 2002. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. *Science,* **296:** 1323–1326.

Arvanitakis, L., Geras Raaka, E., Varma, A., Gershengorn, M.C. & Cesarman, F. 1997. Human herpesvirus KSHV, encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. *Nature,* **385:** 347–350.

Atalay, R., Zimmermann, Z., Wagner, M., Borst, E., Benz, C., Messerle, M. & Hengel, H. 2002. Identification and expression of human cytomegalovirus transcription units coding for two distinct Fc gamma receptor homologs. *Journal of Virology,* **76:** 8596–8608.

Beck, S. & Barrell, B.G. 1988. Human cytomegalo-virus encodes a glycoprotein homologous to MHC class-I antigens. *Nature,* **331:** 269–272.

Benedict, C.A., Butrovich, K.D., Lurain, N.S., Corbeil, J., Rooney, I., Schneider, P., Tschopp, J. & Ware, C.F. 1999. Cutting edge: A novel viral TNF receptor superfamily member in virulent strains of human cytomegalovirus. *Journal of Immunology,* **162:** 6967–6970.

Benedict, C.A., Norris, P.S. & Ware, C.F. 2002. To kill or be killed: viral evasion of apoptosis. *Nature Immunology,* **3:** 1013–1018.

Benedict, C.A., Norris, P.S., Prigozy, T.I., Bodmer, J.L., Mahr, J.A., Garnett, C.T., Martinon, F., Tschopp, J., Gooding, L.R. & Ware, C.F. 2001. Three adenovirus E3 proteins cooperate to evade apoptosis by tumor necrosis factor-related apoptosis-inducing ligand receptor-1 and -2. *Journal of Biological Chemistry,* **276:** 3270–3278.

Bennett, E.M., Bennink, J.R., Yewdell, J.W. & Brodsky, F.M. 1999. Cutting edge: Adenovirus E19 has two mechanisms for affecting class-I MHC expression. *Journal of Immunology,* **162:** 5049–5052.

Bertin, J., Armstrong, R.C., Ottilie, S., Martin, D.A., Wang, Y., Banks, S., Wang, G.H., Senkevich, T.G., Alnemri, E.S., Moss, B., Lenardo, M.J., Tomaselli, K.J. & Cohen, J.I. 1997. Death effector domain-containing herpesvirus and poxvirus proteins inhibit both Fas- and TNFR1-induced apoptosis. *Proceedings of the National Academy of Sciences, USA,* **94:** 1172–1176.

Bertin, J., Mendrysa, S.M., LaCount, D.J., Gaur, S., Krebs, J.F., Armstrong, R.C., Tomaselli, K.J. & Friesen, P.D. 1996. Apoptotic suppression by baculovirus P35 involves cleavage by and inhibition of a virus-induced CED-3/ICE-like protease. *Journal of Virology,* **70:** 6251–6259.

Bodaghi, B., Jones, T.R., Zipeto, D., Vita, C., Sun, L., Laurent, L., Arenzan-Seisdedos, F., Virelizier, J.L. & Michelson, S. 1998. Chemokine sequestration by viral chemoreceptors as a novel viral escape strategy: Withdrawal of chemokines from the environment of cytomegalovirus-infected cells. *Journal of Experimental Medicine,* **188:** 855–866.

Boname, J.M. & Stevenson, P.G. 2001. MHC class I ubiquitination by a viral PHD/LAP finger protein. *Immunity,* **15:** 627–636.

Born, T.L., Morrison, L.A., Esteban, D.J., Van den Bos, T., Thebeau, L.G., Chen, N.H., Spriggs, M.K., Sims, J.E. & Buller, R.M.L. 2000. A poxvirus protein that binds to and inactivates IL-18, and inhibits NK cell response. *Journal of Immunology,* **164:** 3246–3254.

Boshoff, C., Endo, Y., Collins, P.D., Takeuchi, Y., Reeves, J.D., Schweickart, V.L., Siani, M.A., Sasaki, T., Williams, T.J., Gray, P.W., Moore, P.S., Chang, Y. & Weiss, R.A. 1997. Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. *Science,* **278:** 290–294.

Bryant, N.A., Davis-Poynter, N., Van der Plasschen, A. & Alcami, A. 2003. Glycoprotein G isoforms from some alpha herpesviruses function as broad-spectrum chemokine binding proteins. *EMBO Journal,* **22:** 833–846.

Burgert, H.G. & Kvist, S. 1987. The E3/19K protein of adenovirus type-2 binds to the domains of histocompatibility antigens required for CTL recognition. *EMBO Journal,* **6:** 2019–2026.

Chacon, M.R., Almazan, F., Nogal, M.L., Vinuela, E. & Rodriguez, J.F. 1995. The African swine fever virus IAP homolog is a late structural polypeptide. *Virology,* **214:** 670–674.

Chehimi, J., Bandyopodhyay, S., Prakash, K., Perussia, B., Hassan, N.F., Kawashima, H., Campbell, D., Kornbuth, J. & Starr, S.E. 1991. *In vitro* infection of natural killer cells with different human immunodeficiency virus type 1 isolates. *Journal of Virology,* **65:** 1812–1822.

Cho, Y.S., Kang, J.W., Cho, M., Cho, C.W., Lee, S., Choe, Y.K., Kim, Y., Choi, I., Park, S.N., Kim. S., Dinarello, C.A. & Yoon, D.Y. 2001. Down modulation of IL-18 expression by human papillomavirus type 16 E6 oncogene via binding to IL-18. *FEBS Letters,* **501:** 139–145.

Clem, R.J. 2001. Baculoviruses and apoptosis: the good, the bad, and the ugly. *Cell Death and Differentiation,* **8:** 137–143.

Clem, R.J., Fechheimer, M. & Miller, L.K. 1991. Prevention of apoptosis by a baculovirus gene during infection of insect cells. *Science,* **254:** 1388–1390.

Cohen, G.B., Gandhi, R.T., Davis, D.M., Mandelboim, O., Chen, B.K., Strominger, J.L. & Baltimore, D. 1999. The selective downregulation of class I major histocompatibility complex proteins by HIV-1 protects HIV-infected cells from NK cells. *Immunity,* **10:** 661–671.

Colamonici, O.R., Domanski, P., Sweitzer, S.M., Larner, A. & Buller, R.M.L. 1995. Vaccinia virus B18R gene encodes a type-I interferon-binding protein that blocks interferon-alpha transmembrane signaling. *Journal of Biological Chemistry,* **270:** 15974–15978.

Coscoy, L. & Ganem, D. 2001. A viral protein that selectively downregulates ICAM-1 and B7-2 and modulates T cell costimulation. *Journal of Clinical Investigation,* **107:** 1599–1606.

Coscoy, L., Sanchez, D.J. & Ganem, D. 2001. A novel class of herpesvirus-encoded membrane-bound E3 ubiquitin ligases regulates endocytosis of proteins involved in immune recognition. *Journal of Cell Biology,* **155:** 1265–1273.

Cosman, D., Fanger, N., Borges, L., Kubin, M., Chin, W., Peterson, L., Hsu, M.L. 1997. A novel immunoglobulin superfamily receptor for cellular and viral MHC class I molecules. *Immunity,* **7:** 273–282.

Cosman, D., Mullberg, J., Sutherland, C.L., Chin, W., Armitage, R., Fanslow, W., Kubin, M. & Chalupny, N.J. 2001. ULBPs, novel MHC class I-related molecules bind to CMV glycoprotein UL16 and stimulate KN cytotoxicity through the NKG2D receptor. *Immunity,* **14:** 123–133.

Cox, J.H., Bennink, J.R. & Yewdell, J.W. 1991. Retention of adenovirus-E19 glycoprotein in the endoplasmic reticulum is essential to its ability to block antigen presentation. *Journal of Experimental Medicine,* **174:** 1629–1637.

Cretney, E., Degli-Esposti, M.A., Densley, E.H., Farrell, H.E., Davis-Poynter, N.J. & Smyth, M.J. 1999. m144, a murine cytomegalovirus (MCMV)-encoded major histocompatibility complex class I homologue, confers tumor resistance to natural killer cell-mediated rejection. *Journal of Experimental Medicine,* **190:** 435–444.

Crook, N.E., Clem, R.J. & Miller, L.K. 1993. An apoptosis-inhibiting baculovirus gene with a zinc finger-like motif. *Journal of Virology,* **67:** 2168–2174.

Crotta, S., Stilla, A., Wack, A., D'Andrea, A., Nuti, S., D'Oro, U., Mosca, M., Filliponi, F., Brunnetto, R.M., Bonino, F., Abrignani, S. & Valiante, N.M. 2002. Inhibition of natural killer cells through engagement of CD81 by the major hepatitis C envelope protein. *Journal of Experimental Medicine,* **195:** 35–41.

Davis-Poynter, N.J., Lynch, D.M., Vally, H., Shellam, G.R., Rawlinson, W.D., Barrell, B.G. & Farrell, H.E. 1997. Identification and characterization of a G-protein-coupled receptor homolog encoded by murine cytomegalovirus. *Journal of Virology,* **71:** 1521–1529.

Dbaibo, G.S. & Hannun, Y.A. 1998. Cytokine response modifier A (CrmA): A strategically deployed viral weapon. *Clinical Immunology and Immunopathology,* **86:** 134–140.

Deane, D., McInnes, C.J., Percival, A., Wood, A., Thomson, J., Lear, A., Gilray, J., Fleming, S., Mercer, A. & Haig, D. 2000. Orf virus encodes a novel secreted protein inhibitor of granulocyte-macrophage colony-stimulating factor and interleukin-2. *Journal of Virology,* **74:** 1313–1320.

Derfuss, T., Fickenscher, H., Kraft, M.S., Henning, G., Lengenfelder, D., Fleckenstein, B. & Meinl, E. 1998. Antiapoptotic activity of the herpesvirus saimiri-encoded Bcl-2 homolog: Stabilization of mitochondria and inhibition of caspase-3-like activity. *Journal of Virology,* **72:** 5897–5904.

Dobbelstein, M. & Shenk, T. 1996. Protection against apoptosis by the vaccinia virus SPI-2 (B13R) gene product. *Journal of Virology,* **70:** 6479–6485.

Farrell, H.E., Vally, H., Lynch, D.M., Fleming, P., Shellam, G.R., Scalzo, A.A. & Davis Poynter, N.J. 1997. Inhibition of natural killer cells by a cytomegalovirus MHC class I homologue *in vivo. Nature,* **386:** 510–514.

Favoreel, H.W., Nauwynck, H.J., Halewyck, H.M., Van Oostveldt, P., Mettenleiter, T.C. & Pensaert, M.B. 1999. Antibody-induced endocytosis of viral glycoproteins and major histocompatibility complex class I on pseudorabies virus-infected monocytes. *Journal of General Virology,* **80:** 1283–1291.

Favoreel, H.W., Nauwynck, H.J., Van Oostveldt, P., Mettenleiter, T.C. & Pensaert, M.B. 1997. Antibody-induced and cytoskeleton-mediated redistribution and shedding of viral glycoproteins, expressed on pseudorabies virus-infected cells. *Journal of Virology,* **71:** 8254–8261.

Favoreel, H.W., Van de Walle, G.R., Nauwynck, H.J. & Pensaert, M.B. 2003. Virus complement evasion strategies. *Journal of General Virology,* **84:** 1–15.

Fleming, P., Davis-Poynter, N., Degli-Esposti, M., Densley, E., Papadimitriou, J., Shellam, G. & Farrell, H. 1999. The murine cytomegalovirus chemokine homolog, m131/129, is a determinant of viral pathogenicity. *Journal of Virology,* **73:** 6800–6809.

Fleming, S.B., McCaughan, C.A., Andrews, A.E., Nash, A.D. & Mercer, A.A. 1997. A homolog of interleukin-10 is encoded by the poxvirus orf virus. *Journal of Virology,* **71:** 4857–4861.

Fletcher, J.M., Prentice, H.G. & Grundy, J.E. 1998. Natural killer cell lysis of cytomegalovirus (CMV)-infected cells correlates with virally induced changes in cell surface lymphocyte function-associated antigen-3 (LFA-3) expression and not with the CMV-induced down-regulation of cell surface class I HLA. *Journal of Immunology,* **161:** 2365–2374.

Fodor, W.L., Rollins, S.A., Biancocaron, S., Rother, R.P., Guilmette, E.R., Burton, W.V., Albrecht, J.C., Fleckenstein, B. & Squinto, S.P. 1995. The complement control protein homolog of herpesvirus Saimiri regulates serum complement by inhibiting C3 convertase activity. *Journal of Virology,* **69:** 3889–3892.

Friedman, H.M., Cohen, G.H., Eisenberg, R.J., Seidel, C.A. & Cines, D.B. 1984. Glycoprotein-C of herpes simplex virus-1 acts as a receptor for the C3B complement on infected cells. *Nature,* **309:** 633–635.

Galocha, B., Hill, A., Barnett, B.C., Dolan, A., Raimondi, A., Cook, R.F., Brunner, J., McGeoch, D.J. & Ploegh, H.L. 1997. The active site of ICP47, a herpes simplex virus-encoded inhibitor of the major histocompatability complex (MHC)-encoded peptide transporter associated with antigen processing (TAP), maps to the NH2-terminal 35 residues. *Journal of Experimental Medicine,* **185:** 1565–1572.

Gardner, J.D., Tscharke, D.C., Reading, P.C. & Smith, G.L. 2002. Vaccinia virus semaphorin A39R is a 50–55 kDa secreted glycoprotein that affects the outcome of infection in a murine intradermal model. *Journal of General Virology,* **82:** 2083–2093.

Gewurz, B.E., Wang, E.W., Tortorella, D., Schiust, D.J. & Ploegh, H.L. 2001. Human cytomegalovirus US2 endoplasmic reticulum-lumenal domain dictates association with major histocompatibility complex class I in a locus-specific manner. *Journal of Virology,* **75:** 5197–5204.

Gilbert, M.J., Riddell, S.R., Li, C.R. & Greenberg, P.D. 1993. *Journal of Virology*, **67**: 3461–3469.

Glykofrydes, D., Niphuis, H., Kuhn, E.M., Rosenwirth, B., Heeney, J.L., Bruder, J., Niedobitek, G., Muller-Fleckstein, I., Fleckstein, B. & Ensser, A. 2000. Herpesvirus Saimiri vFLIP provides an antiapoptotic function but is not essential for viral replication, transformation, or pathogenicity. *Journal of Virology,* **74:** 11919–11927.

Goldmacher, V.S., Bartle, L.M., Skaletskaya, A., Dionne, C.A., Kedersha, E.S., Vater, C.A., Han, J.W., Lutz, R.J., Watanabe, S., McFarland, E.D.C., Kieff, E.D., Mocarski, E.S. & Chittenden, T. 1999. A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. *Proceedings of the National Academy of Sciences, USA,* **96:** 12536–12541.

Gooding, L.R., Elmore, L.W., Tollefson, A.E., Brady, H.A. & Wold, W.S.M. 1988. A 14,700 mw protein from the E3 region of adenovirus inhibits cytolysis by tumor necrosis factor. *Cell,* **53:** 341–346.

Gooding, L.R., Ranheim, T.S., Tollefson, A.E., Aquino, L., Duerksen-Hughes, P., Horton, T.M. & Wold, W.S.M. 1991. The 10,400-Dalton and 14,500-Dalton proteins encoded by region E3 of adenovirus function together to protect many but not all mouse-cell lines against lysis by tumor-necrosis-factor. *Journal of Virology,* **65:** 4114–4123.

Graham, K.A., Lalani, A.S., Macen, J.L., Ness, T.L., Barry, M., Liu, L.Y., Lucas, A., Clark Lewis, A., Moyer, R.W. & McFadden, G. 1997. The T1/35 kDa family of poxvirus-secreted proteins bind chemokines and modulate leukocyte influx into virus-infected tissues. *Virology,* **229:** 12–24.

Hegde, N.R., Chevalier, M.S., Johnson, D.C. 2003. Viral inhibition of MHC class II antigen presentation. *Trends in Immunology,* **24:** 278–285.

Hegde, N.R., Tomazin, R.A., Wisner, T.W., Dunn, C., Boname, J.M., Lewinsohn, D.M. & Johnson, D.C. 2002. Inhibition of HLA-DR assembly, transport and loading by human cytomegalovirus glycoprotein US3: a novel mechanism for evading major histocompatability complex class II antigen presentation. *Journal of Virology,* **76:** 10929–10941.

Henderson, S., Huen, D., Rowe, M., Dawson, C., Johnson, G. & Rickinson, A. 1993. Epstein-Barr virus-coded BHRF1 protein, a viral homolog of BCL-2, protects human B-cells from programmed cell-death. *Proceedings of the National Academy of Sciences, USA,* **90:** 8479–8483.

Henderson, S., Rowe, M., Gregory, C., Croom-Carter, D., Wang, F., Longnecker, R., Kiefe, E. & Rickinson, A. 1991. Induction of BCL-2 expression by Epstein-Barr-virus latent membrane protein-1 protects infected B-cells from programmed cell-death. *Cell,* **65:** 1107–1115.

Hengel, H., Flohr, T., Hammerling, G.J., Koszinowski, U.H. & Momburg, F. 1996. Human cytomegalovirus inhibits peptide translocation into the endoplasmic reticulum for MHC class I assembly. *Journal of General Virology,* **77:** 2287–2296.

Hengel, H., Koopmann, J.O., Flohr, T., Muranyi, W., Goulmy, E., Hammerling, G.J., Koszinowski, U.H. & Momburg, F. 1997. A viral ER-resident glycoprotein inactivates the MHC-encoded peptide transporter. *Immunity,* **6:** 623–632.

Henry, H., Thomas, A., Shen, Y. & White, E. 2002. Regulation of the mitrochondrial checkpoint in p53-mediated apoptosis confers resistance to cell death. *Oncogene,* **21:** 748–760.

Hewitt, E.W., Duncan, L., Mufti, D., Baker, J., Stevenson, P.G. & Lehner, P.J. 2002. Ubiquitylation of MHC class I by the K3 viral protein signals internalization and TSG101-depenedent degradation. *EMBO Journal,* **21:** 2418–2429.

Hinkley, S., Hill, A.B. & Srikumaran, S. 1998. Bovine herpesvirus-1 infection affects peptide transport activity in bovine cells. *Virus Research,* **53:** 91–96.

Hirsch, R.L., Griffin, D.E. & Winkelstein, J.A. 1981. Host modification of Sindbis virus sialic-acid content influences alternative complement pathway activation and virus clearance. *Journal of Immunology,* **127:** 1740–1743.

Howard, J., Justus, D.E., Totmenin, A.V., Shchelkunov, S. & Kotwal, G.J. 1998. Molecular mimicry of the inflammation modulatory proteins (IMPs) of poxviruses: evasion of the inflammatory response to preserve viral habitat. *Journal of Leukocyte Biology,* **64:** 68–71.

Hsu, D.H., Malefyt, R.D., Fiorentino, D.F., Dang, M.N., Vieira, P., DeVries, J., Spits, H., Mosmann, T.R. & Moore, K.W. 1990. Expression of interleukin-10 activity by Epstein-Barr virus protein BCRF1. *Science,* **250:** 830–832.

Hu, F.Q., Smith, C.A. & Pickup, D.J. 1994. Cowpox virus contains 2 copies of an early gene encoding a soluble secreted form of the Type-II TNF receptor. *Virology,* **204:** 343–356.

Huemer, H.P., Larcher, C., Littel van den Hurk, S.V. & Babiuk, L.A. 1993. Species selection interaction of alphaherpesvirinae with the unspecific immune-system of the host. *Archives of Virology,* **130:** 353–564.

Inngjerdingen, M., Damaj, B. & Maghazachi, A.A. 2001. Expression and regulation of chemokine receptors in human natural killer cells. *Blood,* **97:** 367–375.

Ishido, S., Choi, J.K., Lee, B.S., Wang, C.Y., DeMaria, M., Johnson, R.P., Cohen, G.B. & Jung J.U. 2000. Inhibition of natural killer cell-mediated cytotoxicity by Kaposi's sarcoma-associated herpesvirus K5 protein. *Immunity,* **13:** 365–374.

Ishido, S., Wang, C.Y., Lee, B.S., Cohen, G.B. & Jung, J.U. 2000. Downregulation of major histocompatibility complex class I molecules by Kaposi's sarcoma-associated herpesvirus K3 and K5 proteins. *Journal of Virology,* **74:** 5300–5309.

Jefferies, W.A. & Burgert, H.G. 1990. E3/19K from adenovirus-2 is an immunosubversive protein that binds to a structural motif regulating the intracellular transport of major histocompatibility complex class-I proteins. *Journal of Experimental Medicine,* **172:** 1653–1664.

Jerome, K.R., Fox, R., Chen, Z., Sears, A.E., Lee, H.Y. & Corey, L. 1999. Herpes simplex virus inhibits apoptosis through the action of two genes, Us5 and Us3. *Journal of Virology,* **73:** 8950–8957.

Johnson, J.M., Nicot, C., Fullen, J., Ciminal, V., Casareto, L., Mulloy, J.C., Jacobson, S. & Franchini, G. 2001. Free major histocompatability complex class I heavy chain is preferentially targeted for degradation by human T-cell leukemia/lymphotropic virus type 1 p12(I) protein. *Journal of Virology,* **75:** 6086–6094.

Jones, T.R., Wiertz, E.J.H.J., Sun, L., Nelson, J.A. & Ploegh, H.L. 1996. Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class-I heavy chains. *Proceedings of the National Academy of Sciences, USA,* **93:** 11327–11333.

Kavanagh, D.G., Gold, M.C., Wagner, M., Koszinowski, U.H. & Hill, A.B. 2001. The multiple immune-evasion genes of murine cytomegalovirus are not redundant: m4 and

m152 inhibit antigen presentation in a complementary and cooperative fashion. *Journal of Experimental Medicine,* **194:** 967–977.

Kavanagh, D.G., Koszinowski, U.H. & Hill, A.B. 2001. The murine cytomegalovirus immune evasion protein m4/gp34 forms biochemically distinct complexes with class-I MHC at the cell surface and in a pre-golgi compartment. *Journal of Immunology,* **167:** 3894–3902.

Kawanishi, M. 1997. Epstein-Barr virus BHRF1 protein protects intestine 407 epithelial cells from apoptosis induced by tumor necrosis factor alpha and anti-Fas antibody. *Journal of Virology,* **71:** 3319–3322.

Kawanishi, M. 1997. Expression of Epstein-Barr virus latent membrane protein 1 protects Jurkat T cells from apoptosis induced by serum deprivation. *Virology,* **228:** 244–250.

Kerkau, T., Bacik, I., Bennink, J.R., Yewdell, J.W., Hunig, T., Schimpl, A. & Schubert, U. 1997. The human immunodeficiency virus type 1 (HIV-1) vpu protein interferes with an early step in the biosynthesis of major histocompatibility complex (MHC) class I molecules. *Journal of Experimental Medicine,* **185:** 1295–1305.

Kledal, T.N., Rosenkilde, M.M., Coulin, F., Simmons, G., Johnsen, A.H., Alouani, S., Power, C.A., Luttichau, H.R., Gerstoft, J., Clapham, P.R., Clark-Lewis, I., Wells, T.N.C. & Schwartz, T.W. 1997. A broad-spectrum chemokine antagonist encoded by Kaposi's sarcoma-associated herpesvirus. *Science,* **277:** 1656–1659.

Kleijnen, M.F., Huppa, J.B., Lucin, P., Mukherjee, S., Farrell, H., Campbell, A.E., Koszinowski, U.H., Hill, A.B. & Ploegh, H.L. 1997. A mouse cytomegalovirus glycoprotein, gp34, forms a complex with folded class I MHC molecules in the ER which is not retained but is transported to the cell surface. *EMBO Journal,* **16:** 685–694.

Kloover, J.S., Grauls, G.E.L.M., Blok, M.J., Vink, C. & Bruggeman, C.A. 2002. A rat cytomegalovirus strain with a disruption of the r144 MHC class I-like gene is attenuated in the acute phase of infection in neonatal rats. *Archives of Virology,* **147:** 813–824.

Kostavasili, I., Sahu, A., Friedman, H.M., Eisenberg, R.J., Cohen, G.H. & Lambris, J.D. 1997. Mechanism of complement inactivation by glycoprotein C of herpes simplex virus. *Journal of Immunology*, 158: 1763–1771.

Kotenko, S.V., Saccani, S., Izotova, L.S., Mirochinitchenko, O.V. & Pestka, S. 2000. Human cytomegalovirus harbors its own unique IL-10 homolog (cmcIL-10). *Proceedings of the National Academy of Sciences, USA,* **97:** 1695–1700.

Kotwal, G.J., Isaacs, S.N., McKenzie, R., Frank, M.M. & Moss, B. 1990. Inhibition of the complement cascade by the major secretory protein of vaccinia virus. *Science,* **250:** 827–830.

Krathwohl, M.D., Hromas, R., Brown, D.R., Broxmeyer, H.E. & Fife, K.H. 1997. Functional characterization of the C-C chemokine-like molecules encoded by molluscum contagiosum virus types 1 and 2. *Proceedings of the National Academy of Sciences, USA,* **94:** 9875–9880.

Krmpotic, A., Busch, D.H., Bubic, I., Gebhardt, F., Hengel, H., Hasan, M., Scalzo, A.A., Koszinowski, U.H. & Jonjic, S. 2002. MCMV glycoprotein gb40 confers virus resistance to CD8(+) T cells and NK cells *in vivo. Nature Immunology,* **3:** 529–535.

Kubin, M., Cassiano, L., Chalupny, J., Chin, W., Cosman, D, Fanslow, W., Mulberg, J., Rousseau, A.M., Ulrich, D. & Armitage, R. 2001. ULBP1, 2, 3: novel MHC class I-related molecules that bind to human cytomegalovirus glycoprotein UL16, activate NK cells. *European Journal of Immunology,* **31:** 1428–1437.

Kubota, A., Kubota, S., Farrell, H.E., Davis Poynter, N. & Takei, F. 1999. Inhibition of NK cells by murine CMV-encoded class I MHC homologue m144. *Cellular Immunology,* **191:** 145–151.

Lane, D.P. & Crawford, L.V. 1979. T-antigen is bound to a host protein in SV-40-transformed cells. *Nature,* **278:** 261–263.

Le Gall, S., Erdtmann, L., Benichou, S., Berlioz-Torrent, C., Liu, L.X., Benarous, R., Heard, J.M. & Schwartz, O. 1998. Nef interacts with the mu subunit of clathrin adaptor complexes and reveals a cryptic sorting signal in MHC I molecules. *Immunity,* **8:** 483–495.

Lee, H.J., Essani, K. & Smith, G.L. 2001. The genome sequence of Yaba-like disease virus. a yatapoxvirus. *Virology,* **281:** 170–92.

Lee, S.J., Cho, Y.S., Cho, M.C., Shim, J.H., Lee, K.A., Ko, Y.K., Park, S.N., Hoshino, T., Kim, S., Dinarello, C.A. & Yoon, D.Y. 2001. Both E6 and E7 oncoproteins of human papillomavirus 16 inhibit IL-18-induced IFN-gamma production in human peripheral blood mononuclear and NK cells. *Journal of Immunology,* **167:** 497–504.

Lehner, P.J., Karttunen, J.T., Wilkinson, G.W.G. & Cresswell, P. 1997. The human cytomegalovirus US6 glycoprotein inhibits transporter associated with antigen processing-dependent peptide translocation. *Proceedings of the National Academy of Sciences, USA,* **94:** 6904–6909.

Leonard, G.T. & Sen, G.C. 1996. Effects of adenovirus E1A protein on interferon signaling. *Virology,* **224:** 25–33.

Leong, C.C., Chapman, T.L., Bjorkman, P.J., Formankova, D., Mocarski, E.S., Phillips, J.H. & Lanier, L.L. 1998. Modulation of the natural killer cell cytotoxicity in human cytomegalovirus infection: The role of endogenous class I major histocompatibility complex and a viral class I homolog. *Journal of Experimental Medicine,* **187:** 1681–1687. [See also correction: *ibid.,* **188:** 615.]

Levitskaya, J., Coram, M., Levitsky, V., Imreh, S., Steiger-Waldmullen, P.M., Klein, G., Kurill, M.G. & Masucci, M.G. 1995. Inhibition of antigen processing by the internal repeat region of the Epstein-Barr virus nuclear antigen-1. *Nature,* **375:** 685–688.

Lewandowski, G.A., Lo, D. & Bloom, F.E. 1993. Interference with major histo-compatibility complex class II restricted antigen presentation in the brain by herpes-simplex virus type 1 – A possible mechanism of evasion of the immune response. *Proceedings of the National Academy of Sciences, USA,* **90:** 2005–2009.

Li, Y.G., Kang, J. & Horowitz, M.S. 1998. Interaction of an adenovirus E3 14.7-kiloDalton protein with a novel tumor necrosis factor alpha-inducible cellular protein containing leucine zipper domains. *Molecular and Cellular Biology,* **18:** 1601–1610.

Lilley, B.N., Ploegh, H.L. & Tirabassi, R.S. 2001. Human cytomegalovirus open reading frame TRL11/IRL11 encodes an immunoglobulin G Fc-binding protein. *Journal of Virology,* **75:** 11218–11221.

Linzer, D.I.H. & Levine, A.J. 1979. Characterization of a 54 kDalton cellular SV40 tumor-antigen present in SV40-transformed cells and uninfected embryonal carcinoma-cells. *Cell,* **17:** 43–52.

Loparev, V.N., Parsons, J.M., Knight, J.C., Panus, J.F., Ray, C.A., Buller, R.H.L., Pickup, D.J. & Esposito, J.J. 1998. A third distinct tumor necrosis factor receptor of orthopoxviruses. *Proceedings of the National Academy of Sciences, USA,* **95:** 3786–3791.

Lopez-Botet, M., Llano, M. & Ortega, M. 2001. Human cytomegalovirus and natural killer-mediated surveillance of HLA class I expression: a paradigm of host-pathogen adaptation. *Immunological Reviews,* **181:** 193–202.

Luttichau, H.R., Stine, J., Boesen, T.P., Johnsen, A.H., Chantry, D., Gerstoft, J. & Schwartz, T.W. 2000. A highly selective CC chemokine receptor (CCR)8 antagonist encoded by the poxvirus molluscum contagiosum. *Journal of Experimental Medicine,* **191:** 171–180.

Lybarger, L., Wang, X.L., Harris, M.R., Virgin, H.W. & Hansen, T.H. 2003. Virus subversion of the MHC class I peptide-loading complex. *Immunity,* **18:** 121–130.

Macen, J.L., Graham, K.A., Lee, S.F., Schreiber, M., Boshkov, L.K. & McFadden, G. 1996. Expression of the myxoma virus tumor necrosis factor receptor homologue and M11L genes required to prevent virus-induced apoptosis in infected rabbit lymphocytes. *Virology,* **218:** 232–237.

Machold, R.P., Wiertz, E.J.H.J., Jones, T.R. & Ploegh, H.L. 1997. The HCMV gene products US11 and US2 differ in their ability to attack allelic forms of murine major histocompatibility complex (MHC) class I heavy chains. *Journal of Experimental Medicine,* **185:** 363–366.

Maeda, K., Hayashi, S., Tanioka, Y., Matsumoto, Y. & Otsuka, H. 2002. Pseudorabies virus (PRV) is protected from complement attack by cellular factors and glycoprotein C (gC). *Virus Research,* **84:** 79–87.

Mandelboim, O., Lieberman, N., Lev, M., Paul, L., Arnon, T.I., Bushkin, Y., Davis, D.M., Strominger, J.L., Yewdell, J.W. & Porgador, A. 2001. Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. *Nature,* **409:** 1055–1060.

Marshall, W.L., Yim, C., Gustafson, E., Graf, T., Sage, D.R., Hanify, K., Williams, L., Fingeroth, J. & Finberg, R.W. 1999. Epstein-Barr virus encodes a novel homolog of the bcl-2 oncogene that inhibits apoptosis and associates with Bax and Bak. *Journal of Virology,* **73:** 5181–5185.

Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Buttner, M., Rziha, H.J. & Dehio, C. 1999. A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signalling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases. *EMBO Journal,* **18:** 363–374.

Miller, D.M., Rahill, B.M., Lairmore, M.D., Durbin, J.E., Waldman, W.J. & Sedmark, D.D. 1998. Human cytomegalovirus inhibits major histocompatability complex class II expression by disruption of the Jak/Stat pathway. *Journal of Experimental Medicine,* **187:** 675–683.

Miller, D.M., Zhang, Y.X., Rahill, B.M., Waldman, W.J. & Sedmak, D.D. 1999. Human cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. *Journal of Immunology,* **162:** 6107–6113.

Milne, R.S.B., Mattick, C., Nicholson, L., Devaraj, P., Alcami, A. & Gompels, U.A. 2000. RANTES binding and down-regulation by a novel human herpesvirus-6 beta chemokin receptor. *Journal of Immunology,* **164:** 2396–2404.

Mold, C., Bradt, B.M., Nemerow, G.R. & Cooper, N.R. 1988. Epstein-Barr virus regulates activation and processing of the 3RD component of complement. *Journal of Experimental Medicine,* **168:** 949–969.

Moore, K.W., Viera, P., Fiorentino, D.F., Trounstine, M.L., Khan, T.A. & Mosmann, T.R. 1990. Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. *Science,* **248:** 1230–1234.

Mossman, K., Nation, P., Macen, J., Garbutt, M., Lucas, A. & McFadden, G. 1996. Myxoma virus M-T7. a secreted homolog of the interferon-gamma receptor, is a critical virulence factor for the development of myxomatosis in European rabbits. *Virology,* **215:** 17–30.

Murphy, P.M. 2001. Viral exploitation and subversion of the immune system through chemokine mimicry. *Nature Immunology,* **2:** 116–122.

Nava, V.E., Cheng, E.H.Y., Veliuona, M., Zhou, S.F., Clem, R.J., Mayer, M.L. & Hardwick, J.M. 1997. Herpesvirus Saimiri encodes a functional homolog of the human bcl-2 oncogene. *Journal of Virology,* **71:** 4118–4122.

Neumann, J., Eis-Hubinger, A.M. & Koch, N. 2003. Herpes simplex virus type 1 targets the MHC class II processing pathway for immune evasion. *Journal of Immunology,* **171:** 3075–3083.

Ng, A., Tscharke, D.C., Reading, P.C. & Smith, G.L. 2001. The vaccinia virus A41L protein is a soluble 30 kDa glycoprotein that affects virus virulence. *Journal of General Virology,* **82:** 2095–2105.

Nogal, M.L., de Buitrago, G.G., Rodriguez, C., Cubelos, B., Carrascosa, A.L., Salas, M.L. & Revilla, Y. 2001. African swine fever virus IAP homolog inhibits caspase activation and promotes cell survival in mammalian cells. *Journal of Virology,* **75:** 2535–2543.

Ogata, M. & Shigeta, S. 1979. Appearance of immunoglobulin-GFC receptor in cultured human cells infected with varicella-zoster virus. *Infection and Immunity,* **26:** 770–774.

Oleszak, E.L., Perlman, S., Parr, R., Collisson, E.W. & Leibowitz, J.L. 1993. Molecular mimicry between S peplomer proteins of coronaviruses (MHV, BCV, TGEV and IBV) and Fc receptor. *Advances in Experimental Medicine and Biology*, **342**: 183–188.

Orange, J.S., Fassett, M.S., Koopman, L.A., Boyson, J.E. & Strominger, J.L. 2002. Viral evasion of natural killer cells. *Nature Immunology,* **3:** 1006–1012.

Pan, H. & Griep, A.E. 1995. Temporally distinct patterns of P53-dependent and P53-independent apoptosis during mouse lens development. *Genes and Development,* **9:** 2157–2169.

Panus, J.F., Smith, C.A., Ray, C.A., Smith, T.D., Patel, D.D. & Pickup, D.J. 2002. Cowpox virus encodes a fifth member of the tumor necrosis factor receptor family: A soluble, secreted CD30 homologue. *Proceedings of the National Academy of Sciences, USA,* **99:** 8348–8353.

Parcells, M.S., Lin, S.F., Dienglewicz, R.L., Majerciak, V., Robinson, D.R., Chen, H.C., Wu, Z.N., Dubyak, G.R., Brunovskis, P., Hunt, H.D., Lee, L.F. & Kung, H.J. 2001. Marek's disease virus (MDV) encodes an interleukin-8 homolog (vIL-8): characterization of the vIL-8 protein and a vIL-8 deletion mutant MDV. *Journal of Virology,* **75:** 5159–5173.

Park, B., Oh, H., Lee, S., Song, Y.S., Shin, J., Sung, Y.C., Hwang, S.Y. & Ahn, K. 2002. The MHC class I homolog of human cytomegalovirus is resistant to down-regulation mediated by the unique short region protein (US)2, US3, US6, and US11 gene products. *Journal of Immunology,* **168:** 3464–3469.

Parry, C.M., Simas, J.P., Smith, V.P., Stewart, C.A., Minson, A.C., Efstathoiu, S. & Alcami, A. 2000. A broad spectrum secreted chemokine binding protein encoded by a herpesvirus. *Journal of Experimental Medicine,* **191:** 573–578.

Penfold, M.E.T., Dairaghi, D.J., Duke, G.M., Saederup, N., Mocarski, E.S., Kemble, G.W. & Schall, T.J. 1999. Cytomegalovirus encodes a potent alpha chemokine. *Proceedings of the National Academy of Sciences, USA,* **96:** 9839–9844.

Poggi, A., Carosio, R., Spaggiari, G.M., Fortis, C., Tambussi, G., Dell'Antonio, G., Dal Cin, E., Rubartelli, A. & Zocchi, M.R. 2002. NK cell inactivation by dendritic cells is dependent on LFA-1-mediated induction of calcium-calmodulin kinase II: Inhibition by HIV-1 Tat C-terminal domain. *Journal of Immunology,* **168:** 95–101.

Rakoff-Nahoum, S., Chen, H.C., Kraus, T., George, I., Oei, E., Tyorkin, M., Salik, E., Beuria, P. & Sperber, K. 2001. Regulation of class II expression in monocytic cells after HIV-1 infection. *Journal of Immunology,* **167:** 2331–2342.

Rappocciolo, G., Birch, J. & Ellis, S.A. 2003. Down-regulation of MHC class I expression by equine herpesvirus-1. *Journal of General Virology,* **84:** 293–300.

Reading, P.C., Khanna, A. & Smith, G.L. 2002. Vaccinia virus CrmE encodes a soluble and cell surface tumor necrosis factor receptor that contributes to virus virulence. *Virology,* **292:** 285–298.

Reusch, U., Muranyi, W., Lucin, P., Burgert, H.G., Hengel, H. & Koszinowski, U.H. 199. A cytomegalovirus glycoprotein re-routes MHC class I complexes to lysosomes for degradation. *EMBO Journal,* **18:** 1081–1091.

Reyburn, H.T., Mandelboim, O., Vales Gomez, M., Davis, D.M., Pazmany, L. & Strominger, J.L. 1997. The class I MHC homologue of human cytomegalovirus inhibits attack by natural killer cells. *Nature,* **386:** 514–517.

Rode, H.J., Janssen, W., Rosenwolff, A., Bugert, J.J., Thein, P., Becker, Y. & Darai, G. 1993. The genome of equine herpesvirus type-2 harbors an interleukin-10 (IL10)-like gene. *Virus Genes,* **7:** 111–116.

Rosengard, A.M., Liu, Y., Nie, Z.P. & Jimenez, R. 2002. Variola virus immune evasion design: Expression of a highly efficient inhibitor of human complement. *Proceedings of the National Academy of Sciences, USA,* **99:** 8808–8813.

Rother, R.P., Rollins, S.A., Fodor, W.L., Albrecht, J.C., Setter, E., Fleckenstein, B. & Squinto, S.P. 1994. Inhibition of complement-mediated cytolysis by the terminal complement inhibitor of herpesvirus Saimiri. *Journal of Virology,* **68:** 730–737.

Saederup, N., Aguirre, S.A., Sparer, T.E., Bouley, D.M. & Mocarski, E.S. 2001. Murine cytomegalovirus CC chemokine homolog MCK-2 (m131-129) is a determinant of dissemination that increases inflammation at initial sites of infection. *Journal of Virology,* **75:** 9966–9976.

Saederup, N., Lin, Y.C., Dairaghi, D.J., Schall, T.J. & Mocarski, E.S. 1999. Cytomegalovirus-encoded beta chemokine promotes monocyte-associated viremia in the host. *Proceedings of the National Academy of Sciences, USA,* **96:** 10881–10886.

Saifuddin, M., Parker, C.J., Peeples, M.E., Gorny, M.K., Zollapazner, S., Ghassemi, M., Rooney, I.A., Atkinson, J.P. & Spear, G.T. 1995. Role of virion-associated glycosylphosphatidylinositol-linked proteins CD55 and CD59 in complement resistance of cell line-derived and primary isolates of HIV-L. *Journal of Experimental Medicine,* **182:** 501–509.

Saraiva, M. & Alcami, A. 2001. CrmE, a novel soluble tumor necrosis factor receptor encoded by poxviruses. *Journal of Virology,* **75:** 226–233.

Saraiva, M., Smith, P., Fallon, P.G. & Alcami, A. 2002. Inhibition of type 1 cytokine-mediated inflammation by a soluble CD30 homologue encoded by ectromelia (mousepox) virus. *Journal of Experimental Medicine,* **196:** 829–839.

Sarid, R., Sato, T., Bohenzky, R.A., Russo, J.J. & Chang, Y. 1997. Kaposi's sarcoma-associated herpesvirus encodes a functional Bcl-2 homologue. *Nature Medicine,* **3:** 293–298.

Schindler, M., Wurfl, S., Benaroch, P., Greenough, T.C., Daniels, R., Easterbrook, P., Brenner, M., Munch, J. & Kirchhoff, F. 2003. Down-modulation of mature major histocompatibility complex class II and up-regulation of invariant chain cell surface expression are well-conserved functions of human and simian immunodeficiency virus nef alleles. *Journal of Virology,* **77:** 10548–10556.

Schust, D.J., Tortorella, D., Seebach, J., Phan, C. & Ploegh, H.L. 1998. Trophoblast class I major histocompatibility complex (MHC) products are resistant to rapid degradation of the human cytomegalovirus (HCMV) gene products US2 and US11. *Journal of Experimental Medicine,* **188:** 497–503. [See also correction: *ibid.,* **188**: 497.]

Senkevich, T.G. & Moss, B. 1998. Domain structure, intracellular trafficking, and beta 2-microglobulin binding of a major histocompatibility complex class I homolog encoded by molluscum contagiosum virus. *Virology,* **250:** 397–407.

Shisler, J., Yang, C., Walter, B., Ware, C.F. & Gooding, L.R. 1997. The adenovirus E3-10.4K/14.5K complex mediates loss of cell surface Fas (CD95) and resistance to fas-induced apoptosis. *Journal of Virology,* **71:** 8299–8306.

Shisler, J.L. & Moss, B. 2001. Molluscum contagiosum virus inhibitors of apoptosis: The MC159 v-FLIP protein blocks Fas-induced activation of procaspases and degradation of the related MC160 protein. *Virology,* **282:** 14–25.

Skaletskaya, A., Bartle, L.M., Chittenden, T., McCormick, A.L., Mocarski, E.S. & Goldmacher, V.S. 2001. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. *Proceedings of the National Academy of Sciences, USA,* **98:** 7829–7834.

Smith, C.A., Davis, T., Anderson, D., Solam, L., Beckman, M.P., Jerzy, R., Dower, S.K., Cosman, D. & Goodwin, R.G. 1990. A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins. *Science,* **248:** 1019–1023.

Smith, C.A., Davis, T., Wignall, J.M., Din, W.S., Farrah, T., Upton, C., McFadden, G. & Goodwin, R.G. 1991. T2 open reading frame from the Shope fibroma virus encodes a soluble form of the TNF receptor. *Biochemical and Biophysical Research Communications,* **176:** 335–342.

Smith, C.A., Hu, F.Q., Smith, T.D., Richards, C.L., Smolak, P., Goodwin, R.G. & Pickup, D.J. 1996. Cowpox virus encodes a second soluble homologue of cellular TNF receptors, distinct from CrmB, that binds TNF but not LT alpha. *Virology,* **223:** 132–147.

Smith, C.A., Smith, T.D., Smolak, P.J., Friend, D., Hagen, H., Gerhart, M., Park, L., Pickup, D.J., Torrance, D., Mohler, K., Scooley, K. & Goodwin, R.G. 1997. Poxvirus genomes encode a secreted, soluble protein that preferentially inhibits beta chemokine activity yet lacks sequence homology to known chemokine receptors. *Virology,* **236:** 316–327.

Smith, H.R., Idris, A.H. & Yokoyama, W.M. 2001. Murine natural killer cell activation/receptors. *Immunological Reviews,* **181:** 115–125.

Smith, V.P., Bryant, N.A. & Alcami, A. 2000. Ectromelia, vaccinia and cowpox viruses encode secreted interleukin-18-binding proteins. *Journal of General Virology,* **81:** 1223–1230.

Spear, G.T., Lurain, N.S., Parker, C.J., Ghassemi, M., Payne, G.H. & Saifuddin, M. 1995. Host cell-derived complement control proteins CD55 and CD59 are incorporated into the virions of 2 unrelated enveloped viruses – human T-cell leukemia/lymphoma virus type-I (HTLV-I) and human cytomegalovirus (HCMV). *Journal of Immunology,* **155:** 4376–4381.

Spiller, O.B., Morgan, B.P., Tufaro, F. & Devine, D.V. 1996. Altered expression of host-encoded complement regulators on human cytomegalovirus-infected cells. *European Journal of Immunology,* **26:** 1532–1538.

Stine, J.T., Wood, C., Hill, M., Epp, A., Raport, C.J., Schweickart, V.L., Endo, Y., Sasaki, T., Simmons, G., Boshoff, C., Clapham, P., Chang, Y., Moore, P., Gray, P.W. & Chantry, D. 2000. KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells. *Blood,* **95:** 1151–1157.

Strockbine, L.D., Cohen, J.L., Farrah, T., Lyman, S.D., Wagener, F., DuBose, R.F., Armitage, R.J. & Spriggs, M.K. 1998. The Epstein-Barr virus BARF1 gene encodes a novel, soluble colony-stimulating factor-1 receptor. *Journal of Virology,* **72:** 4015–4021.

Stumptner-Cuvelette, P., Morchoisne, S., Dugast, M., Le Gall, S., Raposo, G., Schwartz, O. & Benaroch, P. 2001. HIV-1 Nef impairs MHC class II antigen presentation and surface expression. *Proceedings of the National Academy of Sciences, USA,* **98:** 12144–12149.

Sturzl, M., Hohenadl, C., Zietz, C., Castanos-Velez, E., Wunderlich, A., Ascherl, G., Biberfeld, P., Monini, P., Browning, P.J. & Ensoli, B. 1999. Expression of K13/v-FLIP gene of human herpesvirus 8 and apoptosis in Karposi's sarcoma spindle cells. *Journal of the National Cancer Institute,* **91:** 1725–1733.

Sundararajan, R. & White, E. 2001. E1B 19K blocks Bax oligomerization and tumor necrosis factor alpha-mediated apoptosis. *Journal of Virology,* **75:** 7506–7516.

Sutherland, C.L., Chalupny, N.J. & Cosman, D. 2001. The UL16-binding proteins, a novel family of MHC class I-related ligands for NKG2D, activate natural killer cell functions. *Immunological Reviews,* **181:** 185–192.

Swigut, T., Iafrate, A.J., Muench, J., Kirchhoff, F. & Skowronski, J. 2000. Simian and human immunodeficiency virus Nef proteins use different surfaces to downregulate class I major histocompatibility complex antigen expression. *Journal of Virology,* **74:** 5691–5701.

Teodoro, J.G. & Branton, P.E. 1997. Regulation of p53-dependent apoptosis, transcriptional repression, and cell transformation by phosphorylation of the 55-kiloDalton E1B protein of human adenovirus type 5. *Journal of Virology,* **71:** 3620–3627.

Tewari, M. & Dixit, V.M. 1995. Fas-induced and tumor necrosis factor-induced apoptosis is inhibited by the poxvirus CrmA gene-product. *Journal of Biological Chemistry,* **270:** 3255–3260.

Thale, R., Lucin, P., Schneider, K., Eggers, M. & Koszinowski, U.H. 1994. Identification and expression of a murine cytomegalovirus early gene coding for an FC receptor. *Journal of Virology,* **68:** 7757–7765.

Thomas, M. & Banks, L. 1998. Inhibition of Bak-induced apoptosis by HPV-18 E6. *Oncogene,* **17:** 2943–2954.

Thomas, M. & Banks, L. 1999. Human papillomavirus (HPV) E6 interactions with Bak are conserved amongst E6 proteins from high and low risk HPV types. *Journal of General Virology,* **80:** 1513–1517.

Tidona, C.A. & Darai, G. 1997. The complete DNA sequence of lymphocystis disease virus. *Virology,* **230:** 207–216.

Tomasec, P., Braud, V.M., Rickards, C., Powell, M.B., McSharry, B.P., Gaddola, S., Cerundolo, V., Borysiewicz, L.K., McMicheal, A.J. & Wilkinson, G.W.G. 2000. Surface expression of HLA-E, an inhibitor of natural killer cells, enhanced by human cytomegalovirus gpUL40. *Science,* **287:** 1031–1033.

Tomazin, R., Boname, J., Hegde, N.R., Lewinsohn, D.H., Altschuler, Y., Jones, T.R., Cresswell, P., Nelson, J.A.. Riddell, S.R., & Johnson, D.C. 1999. Cytomegalovirus US2 destroys two components of the MHC class II pathway, preventing recognition by CD4(+) T cells. *Nature Medicine,* **5:** 1039–1043.

Tong, X., Boll, W., Kirchhausen, T. & Howley, P.M. 1998. Interaction of the bovine papillomavirus E6 protein with the clathrin adaptor complex AP-1. *Journal of Virology,* **72:** 476–482.

Tortorella, D., Gewurz, B.E., Furman, M.H., Schust, D.J. & Pleogh, H.L. 2000. Viral subversion of the immune system. *Annual Review of Immunology,* **18:** 861–926.

Tripp, R.A., Jones, L.P., Haynes, L.M., Zheng, H.Q., Murphy, P.M. & Anderson, L.J. 2001. CX3C chemokine mimicry by respiratory syncytial virus G glycoprotein. *Nature Immunology,* **2:** 732–738.

Tseng, C.T. & Klimpel, G.R. 2002. Binding of hepatitis C envelope protein E2 to CD81 inhibits natural killer cell functions. *Journal of Experimental Medicine,* **195:** 43–49.

Tsukahara, T., Kannagi, M., Ohashi, T., Kato, H., Arai, M., Nunez, G., Iwanaga, Y., Yamamoto, N., Ohtani, K., Nakamura, M. & Fujii, M. 1999. Induction of Bcl-x(L) expression by human T-cell leukemia virus type 1 tax through NF-kappa B in apoptosis-resistant T-cell transfectants with tax. *Journal of Virology,* **73:** 7981–7987.

Tulman, E.R., Alfonso, C.L., Lu, Z., Zsak, L., Kutish, G.F. & Rock, D.L. 2001. Genome of lumpy skin disease virus. *Journal of Virology,* **75:** 7122–7130.

Turner, S.J., Silke, J., Kenshole, B. & Ruby, J. 2000. Characterization of the ectromelia virus serpin SPI-2. *Journal of General Virology,* **81:** 2425–2430.

Twardzik, D.R., Brown, J.P., Ranchalis, J.E., Todaro, G.J. & Moss, B. 1985. Vaccinia virus-infected cells release a novel polypeptide functionally related to transforming and epidermal growth factors. *Proceedings of the National Academy of Sciences, USA,* **82:** 5300–5304.

Upton, C., Mossman, K. & McFadden, G. 1992. Encoding of a homolog of the IFN-gamma receptor by myxoma virus. *Science,* **258:** 1369–1372.

Vanderplasschen, A., Mathew, E., Hollinshead, M., Sim, R.B. & Smith, G.L. 1998. Extracellular enveloped vaccinia virus is resistant to complement because of incorporation of host complement control proteins into its envelope. *Proceedings of the National Academy of Sciences, USA,* **95:** 7544–7549.

Wang, E.C.Y., McSharry, B., Retiere, C., Tomasec, P., Williams, S., Borysiewicz, L.K., Braud, V.M. & Wilkinson, G.W.G. 2002. UL40-mediated NK evasion during productive infection with human cytomegalovirus. *Proceedings of the National Academy of Sciences, USA,* **99:** 7570–7575.

Wang, G.H., Bertin, J., Wang, Y., Martin, D.A., Wang, J., Tomaselli, K.J., Armstrong, R.C. & Cohen, J.I. 1997. Bovine herpesvirus 4 BORFE-2 protein inhibits fas- and tumor necrosis factor receptor 1-induced apoptosis and contains death effector domains shared with other gamma-2 herpesviruses. *Journal of Virology,* **71:** 8928–8932.

Wang, G.H., Garvey, T.L. & Cohen, J.I. 1999. The murine gammaherpesvirus-68 M11 protein inhibits Fas- and TNF-induced apoptosis. *Journal of General Virology,* **80:** 2737–2740.

Wang, X.W., Gibson, M.K., Vermeulen, W., Yeh, H., Forrester, K., Sturzbecher, H.W., Hoiejmakers, J.H.J. & Harris, C.C. 1995. Abrogation of P53-induced apoptosis by the hepatitis-B virus-X gene. *Cancer Research,* **55:** 6012–6016.

Watkins, J.F. 1964. Adsorption of sensitized sheep erythrocytes to HeLa cells infected with herpes simplex virus. *Nature,* **202:** 1364–1365.

Wiertz, E.J.H.J., Tortorella, D., Bogyo, M., Yu, J., Mothes, W., Jones, T.R., Rapoport, T.A. & Ploegh, H.L. 1996. Sec61-mediated transfer of a membrane protein from the endoplasmic reticulum to the proteasome for destruction. *Nature,* **384:** 432–438.

Wolf, D., Witte, V., Laffert, B., Blume, K., Stromer, E., Trapp, S., D'Aloja, P., Schurmann, A. & Baur, A.S. 2001. HIV-1 Nef associated PAK and PI3-kinases stimulate Akt-independent Bad-phosphorylation to induce anti-apoptotic signals. *Nature Medicine,* **7:** 1217–1224.

Xiang, Y. & Moss, B. 1999. Identification of human and mouse homologs of the MC51L-53L-54L family of secreted glycoproteins encoded by the molluscum contagiosum poxvirus. *Virology,* **257:** 297–302.

Xiang, Y. & Moss, B. 1999. IL-18 binding and inhibition of interferon gamma induction by human poxvirus-encoded proteins. *Proceedings of the National Academy of Sciences, USA,* **96:** 11537–11542. [See also correction: *ibid.,* **97**: 11673.]

Xu, X.M., Nash, P. & McFadden, G. 2000. Myxoma virus expresses a TNF receptor homolog with two distinct functions. *Virus Genes,* **21:** 97–109.

Yao, Z.B., Fanslow, W.C., Seldin, M.F., Rousseau, A.M., Painter, S.L., Comeau, M.R., Cohen, J.I. & Spriggs, M.K. 1995. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity,* **3:** 811–821.

Yewdell, J.W. & Hill, A.B. 2002. Viral interference with antigen presentation. *Nature Immunology,* **3:** 1019–1025.

Yin, Y., Maoury, B. & Fahraeus, R. 2003. Self-inhibition of synthesis and antigen presentation by Epstein-Barr-virus encoded EBNA1. *Science,* **301:** 1371–1374.

York, I.A. & Johnson, D.C. 1993. Direct contact with herpes simplex virus-infected cells results in inhibition of lymphokine-activated killer cells because of cell-to-cell spread of virus. *Journal of Infectious Diseases,* **168:** 1127–1132.

Zheng, Z.Y. & Zucker-Franklin, D. 1992. Apparent effectiveness of natural killer cells vis-à-vis retrovirus-infected targets. *Journal of Immunology,* **148:** 3679–3685.

Zhou, Q., Snipas, S., Orth, K., Muzio, M., Dixit, V.M. & Salvesen, G.S. 1997. Target protease specificity of the viral serpin CrmA – Analysis of five caspases. *Journal of Biological Chemistry,* **272:** 7797–7800.

Ziegler, H., Thale, R., Lucin, P., Muranyi, W., Flohr, T., Hengel, H., Farrell, H., Rawlinson, W. & Koszinowski, U.H. 1997. A mouse cytomegalovirus glycoprotein retains MHC class I complexes in the ERGIC/cis-Golgi compartment. *Immunity,* **6:** 57–66.

Zocchi, M.R., Rubartelli, A., Morgavi, P. & Poggi, A. 1998. HIV-1 Tat inhibits human natural killer cell function by blocking L-type calcium channels. *Journal of Immunology,* **161:** 2938–2943.

Zou, P., Isegawa, Y., Nakano, K., Haque, M., Horiguchi, Y. & Yamanishi, K. 1999. Human herpesvirus 6 open reading frame U83 encodes a functional chemokine. *Journal of Virology,* **73:** 5926–5933.